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Mass drug administration for malaria (Review)

Poirot E, Skarbinski J, Sinclair D, Kachur SP, Slutsker L, Hwang J

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[Intervention Review]

Mass drug administration for malaria

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ABSTRACT

Background

Mass drug administration (MDA), defined as the empiric administration of a therapeutic antimalarial regimen to an entire population at the same time, has been a historic component of many malaria control and elimination programmes, but is not currently recommended. With renewed interest in MDA and its role in malaria elimination, this review aims to summarize the findings from existing research studies and program experiences of MDA strategies for reducing malaria burden and transmission.

Objectives

To assess the impact of antimalarial MDA on population asexual parasitaemia prevalence, parasitaemia incidence, gametocytaemia prevalence, anaemia prevalence, mortality and MDA-associated adverse events.

Search methods

We searched the Cochrane Infectious Disease Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE+, EMBASE, to February 2013. We also searched CABS Abstracts, LILACS, reference lists, and recent conference proceedings.

Selection criteria

Cluster-randomized trials and non-randomized controlled studies comparing therapeutic MDA versus placebo or no MDA, and uncontrolled before-and-after studies comparing post-MDA to baseline data were selected. Studies administering intermittent preventive treatment (IPT) to sub-populations (for example, pregnant women, children or infants) were excluded.

Data collection and analysis

Two authors independently reviewed studies for inclusion, extracted data and assessed risk of bias. Studies were stratified by study design and then subgrouped by endemicity, by co-administration of 8-aminoquinoline plus schizonticide drugs and by plasmodium species. The quality of evidence was assessed using the GRADE approach.

Main results

Two cluster-randomized trials, eight non-randomized controlled studies and 22 uncontrolled before-and-after studies are included in this review. Twenty-two studies (29 comparisons) compared MDA to placebo or no intervention of which two comparisons were conducted in areas of low endemicity ($\leq 5\%$), 12 in areas of moderate endemicity (6-39%) and 15 in areas of high endemicity ($\geq 40\%$). Ten studies evaluated MDA plus other vector control measures. The studies used a wide variety of MDA regimens incorporating different drugs, dosages, timings and numbers of MDA rounds. Many of the studies are now more than 30 years old.

Areas of low endemicity ($\leq 5\%$)

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Within the first month post-MDA, a single uncontrolled before-and-after study conducted in 1955 on a small Taiwanese island reported a much lower prevalence of parasitaemia following a single course of chloroquine compared to baseline (1 study, *very low quality evidence*). This lower parasite prevalence was still present after more than 12 months (one study, *very low quality evidence*). In addition, one cluster-randomized trial evaluating MDA in a low endemic setting reported zero episodes of parasitaemia at baseline, and throughout five months of follow-up in both the control and intervention arms (one study, *very low quality evidence*).

Areas of moderate endemicity (6-39%)

Within the first month post-MDA, the prevalence of parasitaemia was much lower in three non-randomized controlled studies from Kenya and India in the 1950s (RR 0.03, 95% CI 0.01 to 0.08, three studies, *moderate quality evidence*), and in three uncontrolled before-and-after studies conducted between 1954 and 1961 (RR 0.29, 95% CI 0.17 to 0.48, three studies, *low quality evidence*).

The longest follow-up in these settings was four to six months. At this time point, the prevalence of parasitaemia remained substantially lower than controls in the two non-randomized controlled studies (RR 0.18, 95% CI 0.10 to 0.33, two studies, *low quality evidence*). In contrast, the two uncontrolled before-and-after studies found mixed results: one found no difference and one found a substantially higher prevalence compared to baseline (not pooled, two studies, *very low quality evidence*).

Areas of high endemicity (≥40%)

Within the first month post-MDA, the single cluster-randomized trial from the Gambia in 1999 found no significant difference in parasite prevalence (one study, *low quality evidence*). However, prevalence was much lower during the MDA programmes in three non-randomized controlled studies conducted in the 1960s and 1970s (RR 0.17, 95% CI 0.11 to 0.27, three studies, *moderate quality evidence*), and within one month of MDA in four uncontrolled before-and-after studies (RR 0.37, 95% CI 0.28 to 0.49, four studies, *low quality evidence*).

Four trials reported changes in prevalence beyond three months. In the Gambia, the single cluster-randomized trial found no difference at five months (one trial, *moderate quality evidence*). The three uncontrolled before-and-after studies had mixed findings with large studies from Palestine and Cambodia showing sustained reductions at four months and 12 months, respectively, and a small study from Malaysia showing no difference after four to six months of follow-up (three studies, *low quality evidence*).

8-aminoquinolines

We found no studies directly comparing MDA regimens that included 8-aminoquinolines with regimens that did not. In a crude subgroup analysis with a limited number of studies, we were unable to detect any evidence of additional benefit of primaquine in moderate- and high-transmission settings.

Plasmodium species

In studies that reported species-specific outcomes, the same interventions resulted in a larger impact on *Plasmodium falciparum* compared to *P. vivax*.

Authors' conclusions

MDA appears to reduce substantially the initial risk of malaria parasitaemia. However, few studies showed sustained impact beyond six months post-MDA, and those that did were conducted on small islands or in highland settings.

To assess whether there is an impact of MDA on malaria transmission in the longer term requires more quasi experimental studies with the intention of elimination, especially in low- and moderate-transmission settings. These studies need to address any long-term outcomes, any potential barriers for community uptake, and contribution to the development of drug resistance.

22 March 2019

Update pending

Authors currently updating

The update is due to be published in 2019.

PLAIN LANGUAGE SUMMARY

Administration of antimalarial drugs to whole populations

Malaria is the most important mosquito-borne disease caused by a parasite, accounting for an estimated 660,000 deaths annually. Fortunately, malaria is both preventable and treatable. Several malaria control tools currently exist, and new and innovative approaches are continually under development.

The administration of drugs against malaria to whole populations, termed mass drug administration (MDA), was a component of many malaria elimination programmes in the 1950s, and is once again attracting interest as a malaria elimination tool. As a consequence, it is important to review the currently available literature in order to assess the potential for this strategy to reduce malaria burden and transmission, and to identify gaps in our understanding.

This review assessed the impact of MDA on several malaria-specific outcome measures. Thirty-two studies were included in this review, from sites in Asia, Africa, Europe and the Americas.

The review found that although MDA can reduce the initial risk of malaria-specific outcomes, these reductions are often not sustained. However, a few studies conducted on small islands or in highland areas did show sustained impact more than six months after MDA.

Adverse events were inadequately addressed in most studies. Notable severe drug reactions, including haemolysis, haemoglobinuria, severe anaemia and death, were reported with 8-aminoquinoline plus schizonticide drug co-administration, while severe skin reactions were reported with sulphadoxine-pyrimethamine plus artesunate plus primaquine.

Assessing the true impact of MDA programmes can be a challenge due to the heterogeneity of the study methods employed. Nonetheless, this review can help guide future antimalarial MDA interventions and their evaluation.

BACKGROUND

Description of the condition

Malaria causes an estimated 219 million clinical episodes and 660,000 deaths annually, primarily among young children in sub-Saharan Africa (WHO 2012). Four main species of the malaria parasite infect humans: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. *P. falciparum* and *P. vivax* cause the majority of infections, with *P. falciparum* responsible for most cases of severe and potentially fatal malaria.

Malaria is both preventable and treatable. Prevention efforts have focused on vector control strategies to reduce adult mosquito populations and human-mosquito contact, and to eradicate mosquito breeding grounds. These strategies include the use of insecticide treated nets (ITNs), indoor residual spraying (IRS), larviciding, and environmental management. In addition, treatment strategies in endemic areas frequently combine case management, and the diagnosis and treatment of clinically ill malaria patients, with disease prevention. This involves administering antimalarial drugs to particularly vulnerable population groups, such as pregnant women, infants and non-immune travellers to endemic areas, to prevent clinical disease.

Success in malaria control using these existing tools has led to renewed interest in the possibility of malaria elimination in some countries or regions. Although the Global Malaria Eradication Program of the mid-20th century was ultimately abandoned, current calls for elimination stress the need for new technologies (insecticide delivery systems, new drugs and insecticides, and candidate vaccines) and the revitalization of older strategies (IRS and larviciding). Mass drug administration (MDA) was a component of many malaria elimination programmes during the eradication era, but it is not currently recommended due to concerns about efficacy, logistical feasibility, sustainability and the risk of accelerating drug resistance (WHO 2010). However, these concerns are not supported by firm evidence, particularly in light of the development of new antimalarial drugs (WHO 2007).

Description of the intervention

For nearly a century, antimalarial drugs have been used in a variety of ways to prevent infection. While the aim of early antimalarial drug distribution studies was to interrupt transmission, this was rarely accomplished. The empiric use of antimalarial drugs to prevent malaria can be generally grouped into three, sometimes overlapping categories: 1) chemoprophylaxis, where drugs are administered at suppressive doses throughout the defined period; 2) intermittent preventive treatment (IPT), where a full curative dose of an antimalarial is given to a target population at specified times; or 3) MDA, where drugs are administered to the whole population either using full therapeutic courses, known as direct MDA, or through the fortification of dietary salt, known as indirect MDA (Greenwood 2004; von Seidlein 2003).

Chemoprophylaxis has been found to be highly effective at reducing mortality and morbidity from malaria in highly endemic areas, but this approach is often difficult to sustain and at times has impaired the development of natural immunity (Greenwood 2004). These difficulties and perceived risks of implementing chemoprophylaxis drove many programmes that began in the

1990s towards targeted drug administration via IPT to populations at high risk of infection (such as pregnant women). There is considerable overlap amongst the three strategies for preventing malaria, and the term MDA has been used to describe varying approaches, from using full therapeutic doses to fortifying foods, and with varying objectives, from decreasing malaria morbidity to interrupting transmission.

Over the past 20 years, MDA has been a key strategy for controlling or eliminating highly-prevalent neglected tropical diseases (NTDs) such as lymphatic filariasis, soil transmitted helminthes, onchocerciasis, schistosomiasis, and trachoma. The simultaneous administration of essential medicines to target high-prevalence NTDs has two main functions: to treat prevalent infection and subsequently to reduce further transmission within the population (Hotez 2009). Mass antimalarial drug administration, defined as the empiric administration of a therapeutic course of an antimalarial regimen to an entire population at the same time without screening or diagnostic testing prior to administration, has been used for malaria control since the early 1930s and was advocated by the World Health Organization (WHO) in the 1950s as a tool in situations where other more conventional control measures had failed (von Seidlein 2003 GMB).

Most early programmes did not clearly define whether their main aim was to interrupt transmission or to control disease. While programmes that attempted to interrupt transmission nearly always failed, there are several examples where MDA, in combination with other malaria control measures, had some success. For instance, MDA with sulfalene-pyrimethamine combined with IRS achieved high levels of initial malaria control during a research project in Garki, Northern Nigeria, in 1969 (Molineaux 1980 NGA). In addition, the use of MDA with other malaria control interventions succeeded in interrupting malaria transmission for both *P. falciparum* and *P. vivax* on the island of Aneityum in Vanuatu (Kaneko 2000 VUT). Primaquine, the only registered drug that can eliminate gametocytes, was given in combination with chloroquine to an estimated 70% of Nicaragua's population in 1981, preventing an estimated 9200 cases of malaria (Garfield 1983 NIC). In these instances, the entire population was simultaneously treated with a therapeutic dose of an antimalarial in a single or multiple rounds both to reduce malaria burden and potentially to interrupt transmission.

How the intervention might work

Malaria transmission is dependent on mosquito vector dynamics, the proportion of humans with peripheral gametocytaemia, and the infectiousness of circulating gametocytes to mosquitoes. MDA of antimalarials might reduce malaria burden by its direct effect on individuals who receive a treatment dose of antimalarials; it may also reduce rates of transmission in several different ways. First, MDA could reduce parasitaemia prevalence and potentially reduce malaria transmission by inhibiting the liver or asexual intra-erythrocytic stages of the parasite, thereby reducing the number of parasites that can progress to form gametocytes. Second, the antimalarial drug could have a direct effect on gametocytes. Third, the antimalarial drug could inhibit the sporogonic cycle in the mosquito. If every member of a given population is treated by antimalarial MDA then one would expect an immediate reduction in asexual parasite prevalence in the population, and possibly a sustained reduction in the population parasite prevalence if there was a concomitant reduction in transmission.

Most antimalarial drugs target the asexual blood stages of the parasite life cycle, as these stages are responsible for symptomatic disease. Blood schizonticidal drugs reduce asexual parasitaemia and possibly early stage gametocytes in *P. falciparum* by preventing the development of mature gametocytes, without having a direct effect on circulating mature gametocytes. Some antimalarial drugs, such as the artemisinins and 8-aminoquinolines (eg primaquine), have known gametocytocidal activities and have the potential to reduce transmission by reducing circulating gametocytaemia.

In addition, primaquine is the only currently available drug with unique activity against mature gametocytes and the hypnozoite stage of *P. vivax* and *P. ovale* species, reducing the possibility of relapse (WHO 2010).

Why it is important to do this review

Since its wider application in the 1950s and 1960s, the use of MDA as a malaria control tool has fallen out of favour due to concerns over its efficacy, logistical feasibility, and sustainability, and over the risk of accelerating drug resistance. But with a renewed interest in malaria elimination, limitations of currently available diagnostic tools, and the development of new antimalarials that have some gametocytocidal effect, such as the artemisinins, MDA is once again being considered as a tool for malaria elimination (Feachem 2009). Given this renewed interest in conducting MDAs, it is important to review the currently available literature to assess the potential for this strategy to reduce malaria burden and transmission. In addition, a systematic review of the literature will allow us to define the gaps in our understanding of the potential benefits and risks of this strategy, such as the risk of adverse drug events in populations given MDA. This information could then guide both the design of future antimalarial MDA interventions and their evaluation.

OBJECTIVES

To assess the impact of antimalarial MDA on population asexual parasitaemia prevalence, parasitaemia incidence, gametocytaemia prevalence, anaemia prevalence, mortality and MDA-associated adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

We assessed randomized and non-randomized studies, including cluster-randomized trials, non-randomized controlled studies and uncontrolled before-and-after studies, that measured at least one outcome of interest in the target population.

Types of participants

Children and adults living in malaria endemic areas. Due to the nature of the intervention, only studies that were carried out on entire populations at the same time were included. Studies where participants left the malaria endemic area during the study period or studies administering IPT to a sub-population, such as pregnant women, children or infants, were excluded.

Types of interventions

Intervention

For the purposes of this review, MDA was defined as the empiric administration of a therapeutic course (doses greater than the

standard prophylactic regimens) of an antimalarial regimen to an entire population at the same time without screening or diagnostic testing prior to administration.

A therapeutic dose was defined as a dose greater than the current standard prophylactic dose (ie chloroquine or amodiaquine at 300 mg of base weekly; pyrimethamine at 25 mg weekly; proguanil at 100 mg daily; mepacrine at 300 mg weekly in one dose or 700 mg weekly in daily doses of 100 mg; and quinine at 325 mg twice a day) (WHO 1951; WHO 1963).

Controls

1. No MDA or placebo for cluster-randomized trials and non-randomized controlled studies.
2. Baseline up to one year prior to intervention for uncontrolled before-and-after studies.

Studies that included other malaria co-interventions (eg ITNs, IRS, source reduction activities and environmental management) and non-malaria co-interventions (eg MDA campaigns for other neglected tropical diseases and mass nutritional supplementation activities such as vitamin A distribution) were included. Studies using an indirect approach to MDA, where antimalarials are added to essential foodstuffs, usually dietary salt, were excluded.

Types of outcome measures

Primary outcomes

1. Parasitaemia prevalence
2. Parasitaemia incidence

Secondary outcomes

1. Gametocytaemia prevalence
2. Anaemia prevalence
3. Mortality
4. Adverse events related to MDA using WHO definitions (Edwards 2000)

Search methods for identification of studies

Electronic searches

Search strategy for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, ongoing).

Databases

We searched the following databases: Cochrane Infectious Disease Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library*; MEDLINE+; EMBASE; CABS Abstracts; and LILACS, using the search strategy detailed in Appendix 1. The final search was conducted on February 6, 2013.

Searching other resources

Reference lists

We checked the reference lists of all studies and articles identified by the above methods, as well as references listed in review articles (Greenwood 2004; von Seidlein 2003; Shanks 2012).

Conference proceedings

We searched the following recent conference proceedings for relevant abstracts: Fifth MIM Pan-African Malaria Conference (Nairobi, Kenya, November 2009); the 58th Annual American Society of Tropical Medicine and Hygiene Conference (Washington, D.C., November 2009); the 59th Annual American Society of Tropical Medicine and Hygiene Conference (Atlanta, G.A., November 2010); the 60th Annual American Society of Tropical Medicine and Hygiene Conference (Philadelphia, P.A., November 2011); and the 61st Annual American Society of Tropical Medicine and Hygiene Conference (Atlanta, G.A., November 2012).

Researchers and organizations

In addition to the electronic searches described above, we contacted additional experts in the field to identify both published and unpublished studies that might be available from other sources.

Data collection and analysis

Selection of studies

Two authors independently screened the titles and abstracts of the search results for potentially relevant studies. We retrieved the full report of any study identified by at least one author as potentially eligible. Two authors then reviewed the full reports of all retrieved studies and independently assessed eligibility using an eligibility form based on the inclusion and exclusion criteria. A third author resolved any discrepancies between the first two authors. We assessed all foreign language papers for eligibility. Excluded studies and the reasons for their exclusion were reported.

Data extraction and management

Using a pre-tested data extraction form, two authors independently extracted information on the study characteristics, including the parasite species of interest, study design, setting (country, transmission season, and endemicity), MDA regimen and coverage, duration of follow-up, methods for ensuring comparability between sites in multi-site studies, and outcomes. We resolved disagreements between the two primary authors by consulting with a third author.

We extracted dichotomous data (parasitaemia prevalence, gametocytaemia prevalence and anaemia) and rate data (parasitaemia incidence and mortality). In all studies, parasite and gametocyte prevalence were assessed by microscopy. Anaemia was defined as per the definition (eg hematocrit < 33%) in the [von Seidlein 2003 GMB](#) study.

Cluster-randomized trials

We extracted clustered-adjusted measures of effect and a standard error when the study was adjusted for clustering. If the study did not adjust for clustering or report the intra-cluster correlation coefficient for dichotomous outcomes, the number of persons with events, the number analyzed and the number randomized in each group was extracted. For count outcomes, we extracted the number of episodes and the person-time risk in each group. The number sampled was calculated as the sum of participants in both the intervention and comparison groups at specified time points.

Non-randomized controlled studies

For non-randomized controlled trials, we extracted the number of persons with events, the number analyzed and the number randomized in each group for dichotomous data. For count outcomes, we extracted the number of episodes and the person time at risk in each group. We included pre-intervention data up to one year prior to the intervention. While all post-MDA data were included, they are reported according to our designated time points (eg < 1 month, 1-3 months, etc). The number sampled was calculated as the sum of participants in both the intervention and comparison groups at specified time points.

Uncontrolled before-and-after studies

For uncontrolled before-and-after studies, we extracted the number of persons with events, the number analyzed and the number in each group for dichotomous data (ie baseline pre-intervention data compared to during MDA or post-MDA measurements). For count outcomes, we extracted the number of episodes and the person time at risk in each group. The number sampled was calculated as the number of participants post-MDA at specified time points.

Assessment of risk of bias in included studies

Two authors independently assessed the risk of bias for both cluster-randomized trials and non-randomized controlled studies and uncontrolled before-and-after studies using an assessment form. We assessed all studies for random sequence generation, allocation concealment, baseline imbalance, contamination protection, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential threats to validity. Authors assessed each element separately and classified as 'low risk of bias', 'high risk of bias' or 'unclear'; details are presented in a separate risk of bias table for each study. In addition, we present a risk of bias summary and a risk of bias graph. We resolved disagreements between the two primary authors by consulting with a third author.

Measures of treatment effect

We reported the findings in a summary of findings table for all outcomes of interest. For cluster-randomized trials and non-randomized controlled studies, we estimated risk ratios between intervention and control groups. For uncontrolled before-and-after studies, we estimated risk ratios against the pre-intervention risk.

We combined reports for specific *Plasmodium* species into one composite malaria outcome for the overall analysis, but conducted a subgroup analysis comparing outcomes for *P. falciparum* and *P. vivax* separately. We adjusted for the contribution of studies with more than one comparison to the overall estimate. Outcomes were reported for all age groups whenever available. However, some studies reported outcomes in children only or in a sample of the treated population.

Unit of analysis issues

Cluster-randomized trials and non-randomized controlled studies

None of the studies reported the design effect or intra-cluster correlation coefficient needed to calculate valid associated variances for the estimates of interest. Thus, we were unable to adjust for clustering.

In addition, non-randomized controlled studies often have few intervention groups/clusters and face the risk of imbalance between groups.

For studies with multiple arms that were included in a meta-analysis more than once, the data was adjusted to account for multiple comparisons.

All estimates were individually analyzed and thus their associated confidence intervals (CIs) need to be cautiously interpreted as unduly narrow.

Uncontrolled before-and-after studies

Similarly, all estimates were individually analyzed and so their associated CIs need to be cautiously interpreted as unduly narrow. Pre-intervention risk was determined from the presented baseline data. When multiple baseline data were presented, the data for the most recent year prior to MDA was used.

Dealing with missing data

It should be noted that for many of the studies MDA was applied widely, although data were only collected on a cross-sectional sample of the entire treated population. Therefore, we have not attempted to apply imputation measures for working with missing data. If data from studies were insufficient, unclear or missing, we attempted to contact study investigators to obtain additional information.

Assessment of heterogeneity

Heterogeneity was assessed by summarizing study and patient characteristics across studies and by inspecting the forest plots for overlapping CIs. The I^2 statistic with a level of 50%, denoting moderate levels of heterogeneity, and the Chi^2 test with a P value of 0.10, indicating statistical significance, were also evaluated to assess heterogeneity.

Assessment of reporting biases

We did not assess publication bias by examining funnel plots for symmetry, since the reported associated variance of the estimates are invalid for the included cluster/population-targeted intervention studies.

Data synthesis

We analyzed data in Review Manager (RevMan) 5.2. Analyses were stratified according to study design (ie cluster-randomized trials, non-randomized controlled studies or uncontrolled before-and-after studies) and by post-intervention time points (ie baseline, during MDA, < 1 month post-MDA, 1-3 months, 4-6 months, 7-12 months, and > 12 months). The during MDA time point refers to situations where MDA occurred over a period of time in multiple rounds. Post-MDA time points were chosen for their ability to assess immediate, intermediate and long-term effects. A random-effects approach was used if heterogeneity was detected; otherwise, a fixed-effect approach was adopted.

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses to explore causes of heterogeneity, grouping by co-interventions (vector control versus no vector control), endemicity level ($\leq 5\%$, 6-39% and $\geq 40\%$), co-administration of 8-aminoquinoline plus schizonticide drug

treatments, and plasmodium species (*P. falciparum* or *P. vivax*). Malaria endemicity classifications of low ($\leq 5\%$), moderate (6-39%), and high ($\geq 40\%$) based on malaria prevalence data at baseline or the control group in children 2-10 years of age were based on the mapping criteria proposed by the Malaria Atlas Project (Hay 2008). Study-specific endemicity was defined preferentially using data from 1) children 2-10 years of age, 2) children of any age, and lastly 3) all ages, depending on the available data. Subgroup analyses to evaluate heterogeneity were not possible for anaemia prevalence and mortality, due to the small number of studies.

Sensitivity analysis

Due to the heterogeneity of the studies, there were not sufficient studies to conduct a sensitivity analysis for investigating the robustness of the results to the risk of bias components.

RESULTS

Description of studies

Results of the search

The initial search was conducted in May 2010, repeated in May 2011 and August 2012, and updated in February 2013. In total, 3048 records were identified through database searches. Of those, 372 abstracts were screened, 240 full-text articles were assessed for eligibility, 48 publications were included in our review, and 32 unique studies were included in our final quantitative meta-analysis. Nine of the studies included more than one comparison (different drugs, number of MDA rounds or co-interventions) resulting in 47 comparisons. One publication has been included as two separate eligible studies (Paik 1974a SLB; Paik 1974b SLB), since it reported interventions in two different geographic settings with differing endemicities. The remaining 192 full-text articles assessed for eligibility were excluded from analysis.

Included studies

Cluster-randomized trials

Two cluster-randomized trials were included: one from a setting with very low endemicity in Tanzania (< 1% prevalence) (Shekalaghe 2011 TZA) and one from a highly endemic setting in the Gambia ($\geq 40\%$ prevalence) (von Seidlein 2003 GMB).

Both studies administered a single treatment course of artesunate plus sulfadoxine-pyrimethamine. In Tanzania, a single dose of primaquine 0.75 mg/kg was also given on day three to all participants excluding pregnant women and those with anaemia at the start of the transmission season; individuals were followed up for four months. In the Gambia study, drugs were given during the transmission season and villages were surveyed weekly for five months. The control group in both trials received a placebo.

Shekalaghe 2011 TZA reports a background rate of bed net use of 25.1% to 36.1% during the study period and an ongoing trachoma control programme; von Seidlein 2003 GMB did not report on ITN or IRS use in the study areas. Shekalaghe 2011 TZA administered the drugs at the start of the transmission season whereas von Seidlein 2003 GMB administered drugs during the transmission season.

Non-randomized controlled studies

We included eight non-randomized controlled studies, of which six were conducted in Africa more than 30 years ago (Escudie

1962 BFA; Jones 1958 KEN; Molineaux 1980 NGA; Najera 1973 NGA; Roberts 1964 KEN; Schneider 1961 BFA), one was from India in the 1950s (Singh 1953 IND) and one was from Vanuatu in the 1990s (Kaneko 2000 VUT). Of the seven studies comparing MDA to no MDA, three studies (seven comparisons) were from high endemicity settings ($\geq 40\%$ prevalence) (Escudie 1962 BFA; Molineaux 1980 NGA; Schneider 1961 BFA) and four studies (five comparisons) were from moderate endemicity settings (6-39% prevalence) (Jones 1958 KEN; Najera 1973 NGA; Roberts 1964 KEN; Singh 1953 IND). Four studies (six comparisons) compared MDA with vector control measures (Kaneko 2000 VUT; Escudie 1962 BFA; Molineaux 1980 NGA; Schneider 1961 BFA).

The drugs used, dosages and frequency, and number of MDA rounds varied across the studies. One study gave a single dose of pyrimethamine (Roberts 1964 KEN) and one study gave pyrimethamine every six months for three rounds (Jones 1958 KEN). One study gave amodiaquine alone every two weeks for five rounds (Singh 1953 IND), one study gave sulfalene-pyrimethamine alone every two to ten weeks for three rounds (Molineaux 1980 NGA) and one study gave chloroquine plus pyrimethamine every two months for 11 rounds (Najera 1973 NGA). Three studies included primaquine in their MDA regimens. Specifically, one study gave chloroquine plus sulfadoxine-pyrimethamine plus primaquine every month for three rounds, with weekly chloroquine and primaquine in the intervening weeks, sufficient to treat vivax hypnozoites (Kaneko 2000 VUT). One study gave chloroquine or amodiaquine, plus single dose primaquine every two weeks for 15 rounds (Schneider 1961 BFA) and one study gave amodiaquine or chloroquine, plus single dose primaquine, every two or four weeks for six months (Escudie 1962 BFA).

Two studies administered drugs during the transmission season (Escudie 1962 BFA; Singh 1953 IND) and two before or at start of the transmission season (Kaneko 2000 VUT; Roberts 1964 KEN). Four studies administered drugs for a longer duration spanning the transmission season (Jones 1958 KEN; Molineaux 1980 NGA; Najera 1973 NGA; Schneider 1961 BFA).

Three studies reported that IRS activities were underway in both intervention and control areas, and allowed estimation of the additive effect of MDA (Escudie 1962 BFA; Molineaux 1980 NGA; Najera 1973 NGA).

Uncontrolled before-and-after studies

The remaining studies (22 out of 32) were uncontrolled before-and-after studies: eight from Africa (Archibald 1960 NGA; Cavalie 1962 CMR; De Zulueta 1961 UGA; De Zulueta 1964 UGA; Gaud 1953 MAR; Houel 1954 MAR; Jones 1954 KEN; Ricosse 1959 BFA), nine from Asia (Hii 1987 MYS; Kondrashin 1985 IND; Malaria_Taiwan 1991 TWN; Metselaar 1961 PNG; Paik 1974a SLB; Paik 1974b SLB; Simeons 1938 IND; Song 2010 KHM; van Dijk 1961 PNG), four from the Americas (Cáceres Garcia 2008 VEN; Comer 1971 PAN; Gabaldon 1959 VEN; Garfield 1983 NIC) and one from Palestine (known as British Mandate Palestine at the time of the study's publication; Kligler 1931 PSE).

Of the 13 studies (15 comparisons) comparing MDA to no intervention, one was conducted in an area of low endemicity ($\leq 5\%$) (Malaria_Taiwan 1991 TWN), seven in areas of moderate endemicity (6-39%) (Archibald 1960 NGA; Cavalie 1962 CMR; Comer 1971 PAN; Houel 1954 MAR; Jones 1954 KEN; Metselaar 1961 PNG;

van Dijk 1961 PNG) and seven in areas of high endemicity ($\geq 40\%$) (Archibald 1960 NGA; Cavalie 1962 CMR; Gaud 1953 MAR; Hii 1987 MYS; Kligler 1931 PSE; Ricosse 1959 BFA; Song 2010 KHM). Six studies evaluated MDA plus vector control measures (De Zulueta 1961 UGA; De Zulueta 1964 UGA; Hii 1987 MYS; Metselaar 1961 PNG; Paik 1974a SLB; Ricosse 1959 BFA). The remaining six studies (Cáceres Garcia 2008 VEN; Gabaldon 1959 VEN; Garfield 1983 NIC; Kondrashin 1985 IND; Paik 1974b SLB; Simeons 1938 IND) only reported monthly incidence estimates ranging from 0.4/1000 to 156/1000. Due to the challenges of converting monthly incidence to precise endemicity estimates, these studies were analyzed separately in the meta-analysis.

Once again, the drugs used, dosages and frequency, and number of rounds varied between studies. In brief, four studies gave pyrimethamine alone (Houel 1954 MAR, once only; Gabaldon 1959 VEN, weekly for six months; Ricosse 1959 BFA, every two weeks for eight rounds; Jones 1954 KEN, every six months for three rounds), six gave pyrimethamine plus chloroquine (Archibald 1960 NGA; Cavalie 1962 CMR; De Zulueta 1961 UGA; De Zulueta 1964 UGA; Metselaar 1961 PNG; Paik 1974a SLB) and one gave amodiaquine alone (Gaud 1953 MAR, once only). The remaining 11 studies all included primaquine or plasmoquine in the MDA regimen. One gave pyrimethamine plus primaquine every two weeks for two years (Comer 1971 PAN), one gave sulfadoxine-pyrimethamine plus primaquine once only (Hii 1987 MYS), four gave chloroquine plus primaquine (Cáceres Garcia 2008 VEN and Garfield 1983 NIC, once only; Kondrashin 1985 IND, every six months for two rounds; Paik 1974b SLB, every three months for three rounds) and one gave artesunate-piperazine plus primaquine (Song 2010 KHM). The two earliest studies gave plasmoquine plus quinine every three weeks for three rounds (Kligler 1931 PSE) and atebirin plus plasmochin once only (Simeons 1938 IND). Two studies administered primaquine with the intention of treating vivax hypnozoites (Cáceres Garcia 2008 VEN; Comer 1971 PAN).

Five studies did not describe the transmission season (Hii 1987 MYS; Malaria_Taiwan 1991 TWN; Metselaar 1961 PNG; Song 2010 KHM; van Dijk 1961 PNG). Six studies administered drugs during the transmission season (Archibald 1960 NGA; Gabaldon 1959 VEN; Houel 1954 MAR; Kligler 1931 PSE; Ricosse 1959 BFA; Simeons 1938 IND), another six at the start or before the transmission season (Cáceres Garcia 2008 VEN; Cavalie 1962 CMR; Garfield 1983 NIC; Gaud 1953 MAR; Kaneko 2000 VUT; Paik 1974a SLB), and four between transmission seasons (Archibald 1960 NGA; Cavalie 1962 CMR; Kondrashin 1985 IND; Paik 1974b SLB). The remaining four studies administered drugs for a longer duration spanning the transmission season (Comer 1971 PAN; De Zulueta 1961 UGA; De Zulueta 1964 UGA; Jones 1954 KEN).

Six studies reported on interventions, which include MDA and co-interventions such as IRS (De Zulueta 1961 UGA; De Zulueta 1964 UGA; Paik 1974a SLB; Ricosse 1959 BFA; Metselaar 1961 PNG) or ITNs (Hii 1987 MYS). These studies have been analyzed separately as they are confounded by the effect of the co-intervention.

Excluded studies

Of the 192 excluded studies, we excluded 74 because they administered an inadequate treatment dose; 19 because they were individually-randomized studies; 16 because they did not provide sufficient information on reported outcomes; and 16 because they did not provide sufficient information on drug administration

(Figure 1). Several studies included in a previous review were excluded due to inadequate treatment doses ([von Seidlein 2003 GMB](#)). [Barber 1932](#) is often cited as the first report of MDA, but it was excluded because plasmoquine simplex 10 mg twice a week

was classified as an inadequate treatment dose ([von Seidlein 2003 GMB](#)). The excluded studies and reasons for their exclusion are given in the '[Characteristics of excluded studies](#)' table.

Figure 1. Study flow diagram.

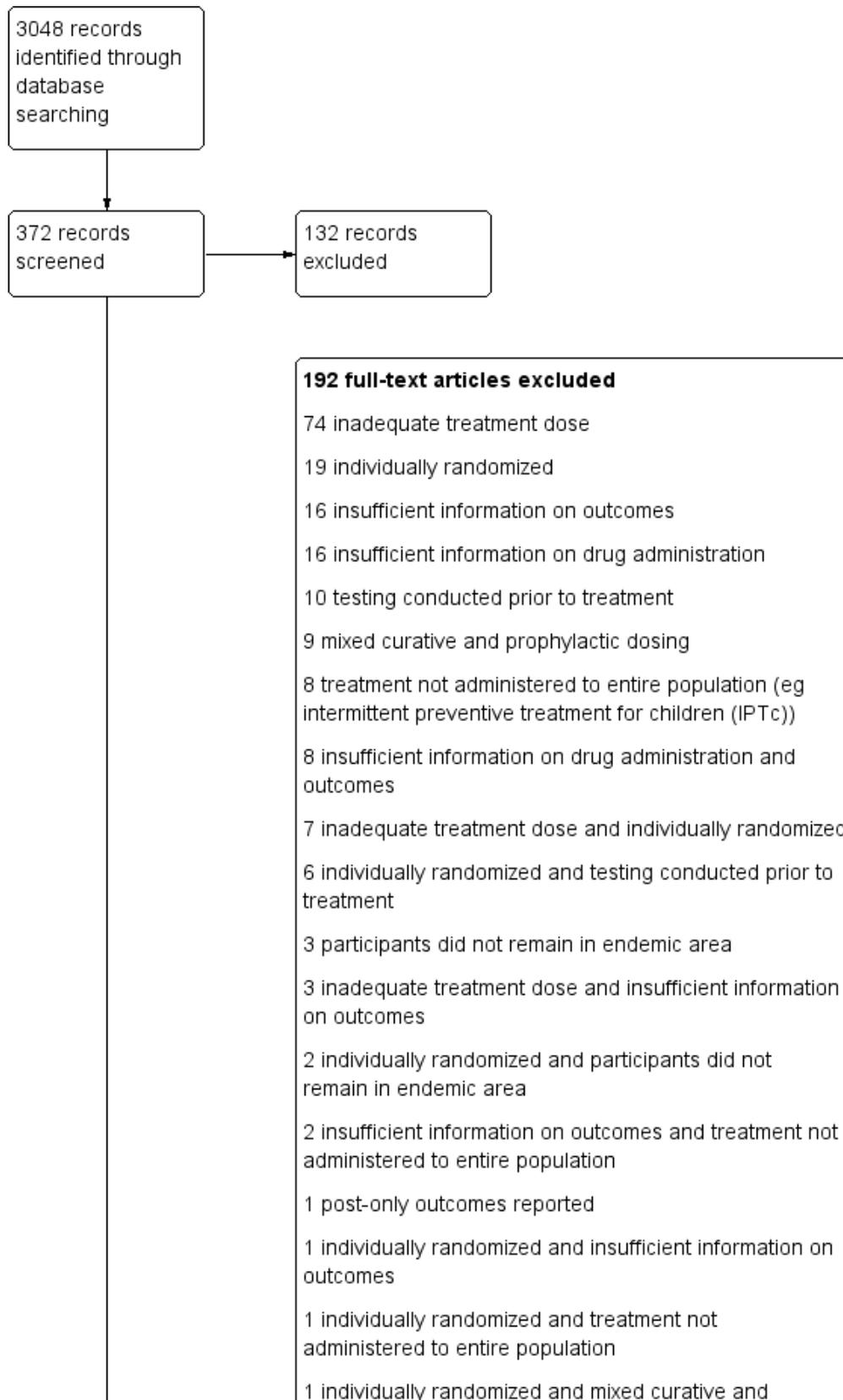


Figure 1. (Continued)



Risk of bias in included studies

The risk of bias assessments are summarized in [Figure 2](#) and [Figure 3](#).

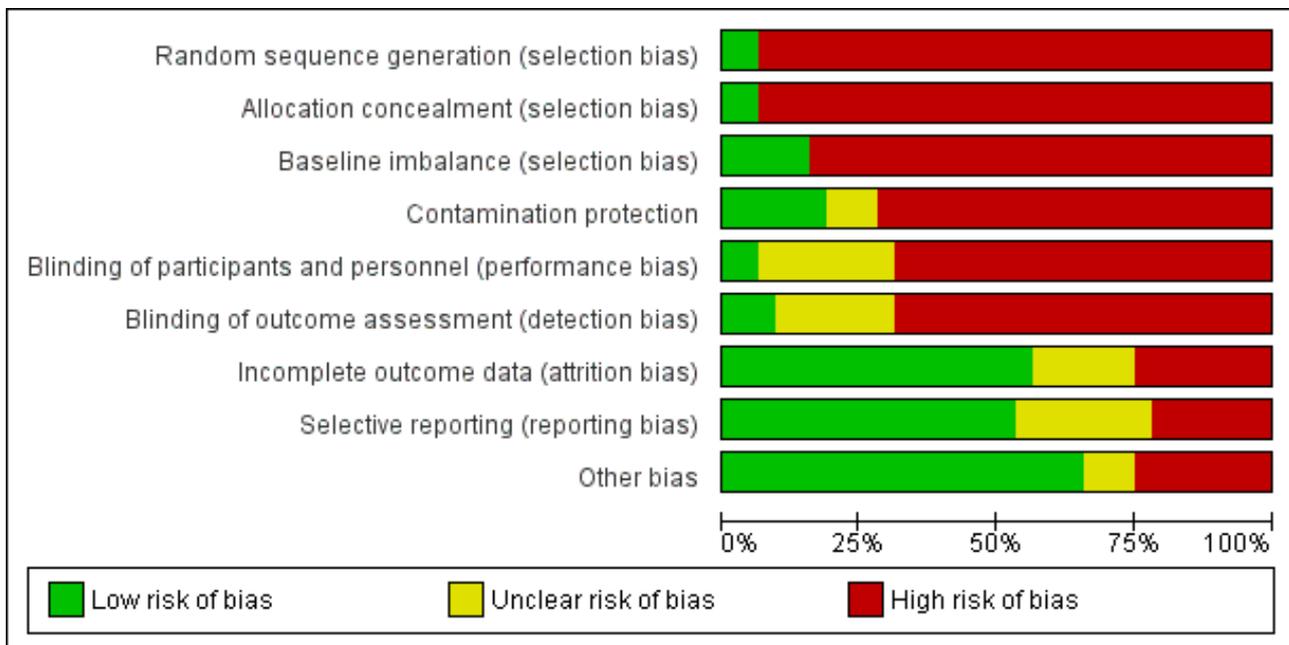
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Baseline imbalance (selection bias)	Contamination protection	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Archibald 1960 NGA	+	-	-	-	-	-	+	-	-
Cáceres Garcia 2008 VEN	+	-	-	-	-	-	+	+	+
Cavalié 1962 CMR	+	-	-	-	-	-	?	?	+
Comer 1971 PAN	+	-	-	-	-	-	+	+	+
De Zulueta 1961 UGA	+	-	-	-	-	-	+	+	+
De Zulueta 1964 UGA	+	-	-	-	-	-	?	+	-
Escudie 1962 BFA	+	-	-	?	?	?	+	+	?
Gabaldon 1959 VEN	+	-	-	-	-	-	+	+	+
Garfield 1983 NIC	+	-	-	-	-	-	+	+	+
Gaud 1953 MAR	+	-	-	-	-	-	?	?	+
Hii 1987 MYS	+	-	-	-	-	-	-	-	+
Houel 1954 MAR	+	-	-	-	-	-	-	?	-
Jones 1954 KEN	+	-	-	-	-	-	+	+	-
Jones 1958 KEN	+	-	-	?	?	?	+	+	-
Kaneko 2000 VUT	+	-	+	+	?	?	+	-	+
Kligler 1931 PSE	+	-	-	-	-	-	-	-	+
Kondrashin 1985 IND	+	-	-	-	-	-	+	?	-
Malaria_Taiwan 1991 TWN	+	-	-	-	-	-	?	+	+
Metselaar 1961 PNG	+	-	-	-	-	-	+	?	+
Molineaux 1980 NGA	+	-	+	+	?	+	+	+	+

Figure 2. (Continued)

Molineaux 1980 NGA	-	-	+	+	?	+	+	+	+
Najera 1973 NGA	-	-	-	+	?	?	+	+	+
Paik 1974a SLB	-	-	-	-	-	-	?	-	-
Paik 1974b SLB	-	-	-	-	-	-	?	?	+
Ricosse 1959 BFA	-	-	-	-	-	-	-	?	-
Roberts 1964 KEN	-	-	-	+	?	?	+	?	+
Schneider 1961 BFA	-	-	+	?	?	?	-	-	?
Shekalaghe 2011 TZA	+	+	+	+	+	+	+	+	+
Simeons 1938 IND	-	-	-	-	-	-	+	+	+
Singh 1953 IND	-	-	-	-	?	?	-	+	+
Song 2010 KHM	-	-	-	-	-	-	-	-	+
van Dijk 1961 PNG	-	-	-	-	-	-	-	+	?
von Seidlein 2003 GMB	+	+	+	+	+	+	+	+	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

The two cluster-randomized trials ([Shekalaghe 2011 TZA](#); [von Seidlein 2003 GMB](#)) adequately randomized and concealed allocation, and are at low risk of selection bias. The non-randomized controlled studies and the uncontrolled before-and-after studies are all considered at high risk of bias for

random sequence generation and allocation concealment due to the non-randomized study design. However, in addition to the two cluster-randomized trials, three non-randomized controlled studies ([Kaneko 2000 VUT](#); [Molineaux 1980 NGA](#); [Schneider 1961 BFA](#)) are at low risk of baseline imbalance between non-randomized groups or clusters. The remaining studies are at

high risk of bias for baseline imbalance due to evident baseline differences between intervention and control groups.

Blinding

The two cluster-randomized trials used placebos and adequately blinded participants and personnel/assessors, and so were judged to be at low risk of performance and detection bias.

In seven non-randomized controlled studies, it was unclear if outcome assessors were blinded to allocation group. One non-randomized controlled study (Molineaux 1980 NGA) did not mention whether participants and personnel were blinded; it was unclear if this impacted the outcomes of interest. However, blood slides in this study were independently re-examined; therefore, risk for detection bias was low. All 22 uncontrolled before-and-after studies were considered to be at high risk of performance bias and detection bias.

Incomplete outcome data

Attrition was low in both of the cluster-randomized trials (Shekalaghe 2011 TZA; von Seidlein 2003 GMB) and were judged to be at low risk of bias. Of the non-randomized controlled studies, two were judged to be at high risk of bias: one study reported that only a subset of participants were included in the evaluation of outcomes (Schneider 1961 BFA) and the other did not report intervention coverage (Singh 1953 IND). The remaining six non-randomized controlled studies demonstrated low risk of bias.

Six uncontrolled before-and-after studies were considered to be at high risk of attrition bias. Two studies had large losses to follow-up (Kligler 1931 PSE; van Dijk 1961 PNG). Furthermore, one study reported that only a subset of participants was included in the evaluation of outcomes (Houel 1954 MAR); one study had to stop MDA distribution in one study zone during the study period, which could impact results (Ricosse 1959 BFA); and one reported missing data (Song 2010 KHM). Hii 1987 MYS was also assessed to be at high risk of bias: although the entire population was treated, only a subset of 286 children were surveyed, of which only 29.7% were present at every one of the eight sessions. An additional six uncontrolled before-and-after studies did not provide a sufficiently adequate description to allow an assessment of attrition bias and these were judged to be 'unclear' (Cavalié 1962 CMR; De Zulueta 1964 UGA; Gaud 1953 MAR; Malaria_Taiwan 1991 TWN; Paik 1974a SLB; Paik 1974b SLB). The other 11 uncontrolled before-and-after studies were at low risk of bias.

Selective reporting

We found evidence of selective outcome reporting in two non-randomized controlled studies (Kaneko 2000 VUT; Schneider 1961 BFA) and five uncontrolled before-and-after studies (Archibald 1960 NGA; Hii 1987 MYS; Kligler 1931 PSE; Paik 1974a SLB; Song 2010 KHM). In addition, one non-randomized controlled trial (Roberts 1964 KEN) and seven uncontrolled before-and-after studies (Cavalié 1962 CMR; Gaud 1953 MAR; Houel 1954 MAR; Kondrashin 1985 IND; Metselaar 1961 PNG; Paik 1974b SLB; Ricosse 1959 BFA) did not contain enough information to assess adequately the risk of selective outcome reporting.

Contamination protection

Contamination protection was low in both of the cluster-randomized trials (Shekalaghe 2011 TZA; von Seidlein 2003 GMB).

Of the eight non-randomized controlled studies, four demonstrated a low risk of contamination (Kaneko 2000 VUT; Molineaux 1980 NGA; Najera 1973 NGA; Roberts 1964 KEN). Another three non-randomized controlled studies (Escudie 1962 BFA; Jones 1958 KEN; Schneider 1961 BFA) did not provide sufficient information to assess whether contamination bias was of concern. However, one study (Singh 1953 IND) did show evidence of contamination, as large numbers of labourers were repatriated to their own villages each week because of high malaria incidence. Due to the lack of a comparison group, all 22 uncontrolled before-and-after studies demonstrated high risk of contamination.

Other potential sources of bias

One non-randomized controlled study (Jones 1958 KEN) and seven uncontrolled before-and-after studies described other sources of potential bias. In one study (Archibald 1960 NGA), anecdotes of ill effects began to circulate and evidence of the 'palming' of tablets was described by investigators. Another study (De Zulueta 1964 UGA) reported that only about half of the population was given treatment during the first administration, with the resultant low coverage likely reducing the impact of the intervention. Houel 1954 MAR provided no data on the coverage of the intervention. An additional three studies (Jones 1954 KEN; Jones 1958 KEN; Ricosse 1959 BFA) described the presence of antimalarial drug resistance. Furthermore, due to the movement of labour, there was likely an influx of *P. falciparum* cases that could have introduced bias in the Kondrashin 1985 IND study. Paik 1974a SLB conducted active case detection in the post-intervention surveillance, which could have resulted in higher baseline prevalence, potentially overestimating the impact of MDA. A further three studies – two non-randomized controlled studies (Escudie 1962 BFA; Schneider 1961 BFA) and one uncontrolled before-and-after study (van Dijk 1961 PNG) – provided insufficient information to assess whether an important risk of bias was present. No other sources of bias were identified in the remaining studies.

Effects of interventions

Section 1: MDA vs no intervention

Comparison 1: MDA vs no MDA in areas of low endemicity ($\leq 5\%$)

Only two studies were conducted in areas of low endemicity ($\leq 5\%$): one cluster-randomized trial (Shekalaghe 2011 TZA) and one uncontrolled before-and-after study (Malaria_Taiwan 1991 TWN). Studies ranged from targeting 1110 (Shekalaghe 2011 TZA) to 1537 (Malaria_Taiwan 1991 TWN) participants in the intervention groups. See Table 1.

Parasitaemia prevalence

Cluster-randomized trials: The study from Tanzania administered a single round of MDA as a 3-day course of artesunate (4 mg/kg/day for three days) plus sulphadoxine-pyrimethamine (25 mg + 1.25 mg/kg as a single dose on the first day) plus primaquine (0.75 mg/kg as a single dose on the third day). All participants in both the intervention and control groups tested negative for malaria parasites at baseline and during the five months of follow-up (1 study, number sampled 484 to 794, Analysis 1.1).

Uncontrolled before-and-after studies: One study from a small, remote island of Taiwan administered MDA as a single dose of chloroquine (12 mg/kg). Compared to baseline data, large reductions in the prevalence of parasitaemia were reported within

the first month post-MDA (RR 0.27, 95% CI 0.14 to 0.50, 1 study, number sampled 1537, [Analysis 1.2](#)) and over several years of post-intervention follow-up (RR 0.02, 95% CI 0.00 to 0.12, 1 study, number sampled 2007, [Analysis 1.2](#)).

Parasitaemia incidence

No studies from settings with low endemicity reported malaria incidence.

Gametocyaemia prevalence

Cluster-randomized trials: In Tanzania, no participants tested positive for gametocytes at baseline or during follow-up (1 study, number sampled 484 to 794, [Analysis 1.3](#)).

Uncontrolled before-and-after studies: The Taiwan study did not report on gametocyaemia prevalence.

Comparison 2: MDA vs no MDA in areas of moderate endemicity (6% to 39%)

Four non-randomized controlled studies (five comparisons) ([Jones 1958 KEN](#); [Najera 1973 NGA](#); [Roberts 1964 KEN](#); [Singh 1953 IND](#)) and seven uncontrolled before-and-after studies ([Archibald 1960 NGA](#); [Cavalié 1962 CMR](#); [Comer 1971 PAN](#); [Houel 1954 MAR](#); [Jones 1954 KEN](#); [Metselaar 1961 PNG](#); [van Dijk 1961 PNG](#)) were conducted in areas of moderate endemicity. Study sample sizes for those targeted in the intervention groups ranged from 125 to 101,000 for non-randomized controlled studies and between 899 and 22,500 for uncontrolled before-and-after studies. See [Table 2](#). One non-randomized controlled study ([Najera 1973 NGA](#)) and four uncontrolled before-and-after studies added MDA to existing IRS programs ([Archibald 1960 NGA](#); [Cavalié 1962 CMR](#); [Houel 1954 MAR](#); [Metselaar 1961 PNG](#)).

Parasitaemia prevalence

Non-randomized controlled studies: There was evidence of baseline imbalance in parasite prevalence in all four studies, biasing the subsequent time points and leading to an over- or underestimate of the effect (4 studies, number sampled 3123, [Analysis 2.1](#)). These studies were conducted between 1952 and 1968 in India, Kenya and Nigeria.

Only one study reported the prevalence of parasitaemia while the MDA was ongoing and this study administered MDA as chloroquine (450mg) plus pyrimethamine (45mg) every two months for 11 rounds ([Najera 1973 NGA](#)). The study reported a substantial reduction in prevalence compared to the control areas (RR 0.27, 95% CI 0.25 to 0.28, 1 study, number sampled 47,014, [Analysis 2.1](#))

Three studies reported very large reductions in prevalence during the first month post-MDA compared to control areas (RR 0.03, 95% CI 0.01 to 0.08, 3 studies, number sampled 1934, [Analysis 2.1](#)). Only two studies from the 1950s conducted follow-up for more than three months post-MDA ([Jones 1958 KEN](#); [Roberts 1964 KEN](#)). In [Jones 1958 KEN](#), the baseline prevalence of parasitaemia was higher in the intervention areas than in control areas, but was substantially lower in the intervention areas one to three months post-MDA (RR 0.22, 95% CI 0.14 to 0.36, 1 study, number sampled 357, [Analysis 2.1](#)) and at about four months post-MDA (RR 0.28, 95% CI 0.21 to 0.38, 1 study, number sampled 410, [Analysis 2.1](#)). This study administered MDA as pyrimethamine (100 mg) every six months for three rounds. In the highlands of Kenya, where MDA

was administered as a single dose of pyrimethamine ([Roberts 1964 KEN](#)), there was evidence of continued reduction compared to the control areas by month 7 of follow-up (RR 0.19, 95% CI 0.11 to 0.33, 1 study, number sampled 600, [Analysis 2.1](#)).

Uncontrolled before-and-after studies: Compared to baseline data, a large reduction in parasitaemia was seen during multiple rounds of pyrimethamine (50 mg) plus primaquine (40 mg) given every two weeks in Panama ([Comer 1971 PAN](#)) and a smaller reduction was seen during weekly administration of chloroquine (450mg) and pyrimethamine (50 mg) for six weeks in New Guinea ([Metselaar 1961 PNG](#)) (RR 0.17, 95% CI 0.02 to 1.47, 2 studies, number sampled 4209, [Analysis 2.2](#)).

Three studies reported parasitaemia within one month of finishing MDA, with large and consistent reductions compared to baseline (RR 0.29, 95% CI 0.17 to 0.48, 3 studies, number sampled 1727, [Analysis 2.2](#)). Two studies conducted follow-up for more than three months post-MDA with mixed results: one found no effect ([Archibald 1960 NGA](#)) and one found a substantial increase in prevalence compared to baseline ([Cavalié 1962 CMR](#)).

Parasitaemia incidence

None of these studies reported on parasitaemia incidence.

Gametocyaemia prevalence

Non-randomized controlled studies: One non-randomized controlled study from Nigeria reported a substantial reduction in gametocyaemia in the intervention area during 11 rounds of chloroquine plus pyrimethamine given every two months (RR 0.48, 95% CI 0.42 to 0.54, 1 study, number sampled 47,014, [Analysis 2.3](#)). A second study from Kenya reported a substantial reduction in prevalence within the first month following three rounds of pyrimethamine (RR 0.28, 95% CI 0.10 to 0.82, 1 study, number sampled 433, [Analysis 2.3](#)). Only the Kenyan study conducted follow-up for longer than three months post-MDA. At four months, gametocyaemia prevalence appeared to be increasing in the intervention population and was no longer substantially different from the control population (1 study, number sampled 410, [Analysis 2.3](#)). Neither of these studies gave primaquine as part of the MDA.

Uncontrolled before-and-after studies: Three uncontrolled before-and-after studies reported on gametocyte prevalence within one month of MDA, with substantial effects in two studies (RR 0.47, 95% CI 0.25 to 0.87, 3 studies, number sampled 1727, [Analysis 2.4](#)). Only one study continued follow-up beyond three months ([Archibald 1960 NGA](#)); in this study, the prevalence of gametocyaemia was rising after five months but remained lower than baseline (1 study, number sampled 125, [Analysis 2.4](#)).

Comparison 3: MDA vs no MDA in areas of high endemicity (≥ 40%)

One cluster-randomized trial ([von Seidlein 2003 GMB](#)), three non-randomized controlled studies (seven comparisons) ([Escudie 1962 BFA](#); [Molineaux 1980 NGA](#); [Schneider 1961 BFA](#)), and seven uncontrolled before-and-after studies ([Archibald 1960 NGA](#); [Cavalié 1962 CMR](#); [Gaud 1953 MAR](#); [Hii 1987 MYS](#); [Kligler 1931 PSE](#); [Ricosse 1959 BFA](#); [Song 2010 KHM](#)) compared MDA with no MDA in areas of high endemicity. Of the 16,442 participants in the [von Seidlein 2003 GMB](#) cluster-randomized trial, 14,017 took part in the MDA trial and 1969 were evaluated in the intervention

group. The population targeted ranged from 1810 to 14,129 for the non-randomized controlled studies and from 148 to 7000 for the uncontrolled before-and-after studies; see [Table 3](#). Two non-randomized controlled studies ([Escudie 1962 BFA](#); [Molineaux 1980 NGA](#)) and two uncontrolled before-and-after studies added MDA to existing IRS programs ([Archibald 1960 NGA](#); [Cavalié 1962 CMR](#)). Several of these studies had multiple treatment arms and so appear more than once in the subsequent analyses.

Parasitaemia prevalence

Cluster-randomized trials: In the Gambia, no significant differences in parasite prevalence were seen at baseline, at six to 10 weeks or at five months following a single treatment course of artesunate plus sulfadoxine-pyrimethamine (1 study, number sampled 1089 to 1800, [Analysis 3.1](#)).

Non-randomized controlled studies: At baseline, there was evidence of imbalance in parasite prevalence between groups in all three studies, biasing the subsequent time points and leading to an overestimate of the effect (RR 0.84, 95% CI 0.70 to 1.00, 3 studies, number sampled 9395, [Analysis 3.2](#)). These studies were conducted between 1960 and 1975.

Even accounting for the baseline differences, large reductions in parasitaemia were seen consistently during multi-round MDA programmes (RR 0.17, 95% CI 0.11 to 0.27, 3 studies, number sampled 12,561, [Analysis 3.2](#)). In Burkina Faso, where MDA was administered as amodiaquine or chloroquine plus primaquine, there was still some evidence of benefit up to three months post-MDA, although this effect was of a smaller magnitude than seen during the MDA programmes (RR 0.52, 95% CI 0.33 to 0.81, 1 study, number sampled 7197, [Analysis 3.2](#)). These two studies demonstrated a lessening effect back towards baseline estimates.

Uncontrolled before-and-after studies: Similarly, in uncontrolled before-and-after studies, substantial reductions in parasitaemia were seen during multi-round MDA programmes (RR 0.10, 95% CI 0.03 to 0.34, 2 studies, number sampled 911, [Analysis 3.3](#)). Reductions were also seen within one month of the MDA programmes finishing (RR 0.37, 95% CI 0.28 to 0.49, 4 studies, number sampled 1941, [Analysis 3.3](#)), although the magnitude of the reduction ranged from 30% to 72%. Three studies continued to monitor prevalence for more than three months post-MDA, with mixed findings. One recent study that administered artesunate plus piperazine with primaquine reported a large reduction over time in Cambodia ([Song 2010 KHM](#)), one 1930 study from Palestine using plasmochin and quinine showed modest reductions, while one small study from Malaysia administering sulfadoxine-pyrimethamine plus primaquine demonstrated no significant effect at any time point ([Hii 1987 MYS](#)). In the Cambodia study, periodic surveys were carried out every six months for two years after the mass treatment programme.

Parasitaemia incidence

Cluster-randomized trials: In the single cluster-randomized trial from the Gambia, the incidence of parasitaemia was reduced by over 50% during the first month following a single course of artesunate plus sulfadoxine-pyrimethamine (RR 0.41, 95% CI 0.23 to 0.74, one study, number sampled 1225, [Analysis 3.4](#)). This significant reduction is consistent with the adjusted geometric mean rate ratio reported in the publication (rate ratio 0.37, 95% CI 0.17 to 0.84) ([von Seidlein 2003 GMB](#)). However, no difference was

present at six to 10 weeks or at five months in both the unadjusted rate ratios presented in this review and the adjusted rate ratios presented in the publication.

Gametocyaemia prevalence

Cluster-randomized trials: In the Gambia, there were no statistically significant differences in gametocyaemia at baseline or at five months following a single treatment course of artesunate plus sulfadoxine-pyrimethamine (1 study, number sampled 1376 to 1414, [Analysis 3.5](#)).

Non-randomized controlled studies: Three non-randomized controlled studies reported substantial reductions in the prevalence of gametocyaemia during MDA programmes (RR 0.17, 95% CI 0.10 to 0.28, 3 studies, number sampled 12,561, [Analysis 3.6](#)). Two of these studies administered MDA as amodiaquine or chloroquine plus primaquine ([Escudie 1962 BFA](#); [Schneider 1961 BFA](#)) and one study gave sulfalene-pyrimethamine alone ([Molineaux 1980 NGA](#)). In [Schneider 1961 BFA](#), the effect on gametocyaemia appeared to be lost within three months of the MDA programme finishing, while in [Escudie 1962 BFA](#) some reduction still remained after three months in three of four comparison arms, although the impact decreased in magnitude.

Uncontrolled before-and-after studies: Five uncontrolled before-and-after studies reported on the effect of MDA on gametocyaemia prevalence. Two studies either administered pyrimethamine alone ([Ricosse 1959 BFA](#)) or chloroquine plus pyrimethamine ([Archibald 1960 NGA](#)). Two studies were carried out in Asia and treated individuals with a combination drug of sulfadoxine-pyrimethamine plus primaquine ([Hii 1987 MYS](#)) or with artemisinin and piperazine given with primaquine every 10 days ([Song 2010 KHM](#)). One study used plasmochin and quinine ([Kligler 1931 PSE](#)). Only [Song 2010 KHM](#) demonstrated sustained impact after six months (RR 0.19, 95% CI 0.13 to 0.27, 1 study, number sampled 1609, [Analysis 3.7](#)), which was sustained during the 30 month follow-up (RR 0.09, 95% CI 0.05 to 0.15, 1 study, number sampled 1175, [Analysis 3.7](#)).

Anaemia prevalence

Cluster-randomized trials: The prevalence of anaemia (hematocrit < 33%) was only reported in a single cluster-randomized trial from the Gambia ([von Seidlein 2003 GMB](#)). This study demonstrated a modest reduction in anaemia prevalence at five months post-MDA (RR 0.84, 95% CI 0.75 to 0.93, 1 study, number sampled 1414, [Analysis 3.8](#)).

Mortality

Cluster-randomized trials: Mortality was only reported in a single cluster-randomized trial from the Gambia ([von Seidlein 2003 GMB](#)). Mortality was low in both study arms over five months follow-up, with no statistically significant difference between the two groups (1 study, number sampled 3655, [Analysis 3.9](#)).

Section 2: MDA + vector control vs no intervention

Comparison 4: MDA plus vector control vs no intervention in areas of moderate endemicity (6% to 39%)

One non-randomized controlled study ([Kaneko 2000 VUT](#)) and four uncontrolled before-and-after studies ([De Zulueta 1961 UGA](#); [De Zulueta 1964 UGA](#); [Paik 1974a SLB](#); [Ricosse 1959 BFA](#)) compared MDA plus vector control with no intervention in areas of moderate endemicity. The target population for the [Kaneko 2000 VUT](#) study

was 718 villagers. The target population for three uncontrolled before-and-after studies (De Zulueta 1961 UGA; De Zulueta 1964 UGA; Ricosse 1959 BFA) ranged from 5000 to 59,605; in the Paik 1974a SLB study, the targeted population was not described. See Table 4.

Parasitaemia prevalence

Non-randomized controlled studies: Kaneko 2000 VUT included larvivorous fish in several identified breeding sites and universal coverage with insecticide-treated bed nets (about 0.94 nets per villager) in its intervention group. In the comparison group, bed net coverage was approximately 20%. Twelve months post-MDA, the prevalence of parasitaemia was 1% in the intervention island compared to 12% in the control island (Analysis 4.1).

Uncontrolled before-and-after studies: These four studies administered MDA with either pyrimethamine alone (Ricosse 1959 BFA) or chloroquine plus pyrimethamine (De Zulueta 1961 UGA; De Zulueta 1964 UGA; Paik 1974a SLB), together with IRS. The greatest effect on parasitaemia prevalence was seen within one month post-MDA (RR 0.06, 95% CI 0.01 to 0.33, three studies, number sampled 2961, Analysis 4.2), which was larger than the effect seen in Analysis 2.2 with MDA alone. Only one study (De Zulueta 1964 UGA) from the Ugandan highlands with disappearance of the vector with IRS found a sustained, large effect lasting over 12 months (RR 0.00, 95% CI 0.00 to 0.03, one study, number sampled 1229, Analysis 4.2).

Gametocyaemia prevalence

Uncontrolled before-and-after studies: Two studies from Uganda (De Zulueta 1961 UGA) and Burkina Faso (Ricosse 1959 BFA) demonstrated a reduction in gametocyaemia prevalence during MDA (RR 0.13, 95% CI 0.06 to 0.27, two studies, number sampled 2479, Analysis 4.3). Only Ricosse 1959 BFA reported estimates for gametocyaemia prevalence post-MDA. The largest effect was seen within one month of administration (RR 0.01, 95% CI 0.00 to 0.16, one study, number sampled 919, Analysis 4.3), with a lessening effect after two months (RR 0.22, 95% CI 0.11 to 0.41, one study, number sampled 953, Analysis 4.3). Neither of these studies administered primaquine as part of MDA.

Comparison 5: MDA plus vector control vs no intervention in areas of high endemicity ($\geq 40\%$)

Three non-randomized controlled studies (five comparisons) (Escudie 1962 BFA; Molineaux 1980 NGA; Schneider 1961 BFA) and two uncontrolled before-and-after studies (Hii 1987 MYS; Metselaar 1961 PNG) compared MDA plus vector control with no intervention in settings of high endemicity. The number of participants ranged from 1810 to 14,129 in the non-randomized controlled studies and from 754 to 2500 participants in the two uncontrolled before-after studies. See Table 4.

Parasitaemia prevalence

Non-randomized controlled studies: These studies administered MDA at intervals of two weeks to 10 weeks for between eight and 23 rounds, alongside IRS. These studies were conducted between 1961 and 1975. In two studies (Escudie 1962 BFA; Schneider 1961 BFA), there was evidence of baseline imbalance in parasite prevalence, biasing the subsequent time points and leading to an overestimate of the effect (Analysis 5.1). Despite this, MDA plus IRS appeared to reduce parasitaemia substantially during MDA (RR 0.10, 95% CI 0.06 to 0.16, three studies, number sampled 9493, Analysis

5.1). However, by three months post-MDA, this effect had lessened in both Schneider 1961 BFA and Escudie 1962 BFA compared to during administration (RR 0.12, 95% CI 0.06 to 0.23, two studies, number sampled 4455, Analysis 5.1). The effect on parasitaemia prevalence both during and one to three months post MDA with IRS were larger than noted in studies without concomitant vector control measures (Analysis 3.2). Only one study (Molineaux 1980 NGA) conducted follow-up for more than three months, reporting a continued reduction in prevalence with a modest effect from seven to 12 months (RR 0.60, 95% CI 0.55 to 0.67, one study, number sampled 3154, Analysis 5.1).

Uncontrolled before-and-after studies: A study (Hii 1987 MYS) from Malaysia issuing permethrin-impregnated bed nets to all households along with larval control measures and a study (Metselaar 1961 PNG) from New Guinea conducting IRS reported the impact on parasitaemia prevalence. The largest reduction in parasitaemia was seen one to three months post MDA (RR 0.13, 95% CI 0.01 to 2.51, two studies, number sampled 2722, Analysis 5.2), with lessening effect as the post-intervention time increased. Compared to baseline, no difference was noted after nine months of follow-up for the Malaysian study (Analysis 5.2).

Gametocyaemia prevalence

Non-randomized controlled studies: All three studies (Escudie 1962 BFA; Molineaux 1980 NGA; Schneider 1961 BFA), comprising five comparison groups, included IRS in addition to MDA. At baseline, two studies with three comparison groups (Escudie 1962 BFA; Schneider 1961 BFA) demonstrated higher gametocyaemia prevalence in the intervention arms compared to the comparison arms. These baseline imbalances could inflate the impact of the effect at subsequent time points. Despite this, MDA appeared to reduce substantially the prevalence of gametocyaemia during the intervention (RR 0.08, 95% CI 0.03 to 0.20, three studies, number sampled 9493, Analysis 5.3). The effect of MDA on gametocyaemia prevalence remained until three months post-MDA (RR 0.08, 95% CI 0.05 to 0.14, two studies, number sampled 4455, Analysis 5.3). Only one study from Nigeria (Molineaux 1980 NGA) reported long-term data. This study administered MDA using sulfalene (500 mg) plus pyrimethamine (25 mg) every 10 weeks, and noted lessening effect between seven and 11 months (RR 0.87, 95% CI 0.73 to 1.05, one study, number sampled 3154) and no difference beyond 12 months of follow-up (RR 0.96, 95% CI 0.81 to 1.14, one study, number sampled 3261, Analysis 5.3).

Uncontrolled before-and-after studies: A single study (Hii 1987 MYS) reporting the co-administration of ITNs demonstrated a reduction in gametocyaemia prevalence during MDA (RR 0.29, 95% CI 0.17 to 0.50, one study, number sampled 219, Analysis 5.4). The impact on gametocyaemia prevalence decreased with increased time post-intervention. After six months, estimates of prevalence in the intervention villages approached those before intervention (RR 0.93, 95% CI 0.65 to 1.33, one study, number sampled 194, Analysis 5.4).

Section 3: Parasitaemia incidence only studies

Six uncontrolled before-and-after studies (Cáceres García 2008 VEN; Gabaldon 1959 VEN; Garfield 1983 NIC; Kondrashin 1985 IND; Paik 1974b SLB; Simeons 1938 IND) only reported baseline monthly incidence and did not provide malaria endemicity estimates (Table 5). Among these, four compared MDA with no intervention (Cáceres García 2008 VEN; Gabaldon 1959 VEN; Kondrashin 1985 IND; Paik

1974b SLB), while the remaining two compared MDA plus vector control with no intervention (Garfield 1983 NIC; Simeons 1938 IND). Targeted populations ranged in size from 1200 to 2,300,000.

Comparison 6.1: MDA vs no MDA

Uncontrolled before-and-after studies: Compared to baseline, large reductions in parasitaemia incidence were seen during MDA administration in two studies - one from Venezuela where pyrimethamine was administered in 24 weekly rounds (Gabaldon 1959 VEN) and another from the Solomon Islands (known as the British Solomon Islands at the time of the study's publication) where three rounds of chloroquine plus primaquine were given three months apart (Paik 1974b SLB). In contrast, no significant effect was seen in India during two rounds of chloroquine plus primaquine given six months apart (Kondrashin 1985 IND) (Analysis 6.1). In addition, three additional studies found large reductions in incidence within the first month post-intervention (Cáceres García 2008 VEN; Gabaldon 1959 VEN; Paik 1974b SLB), although this effect reduced over the following one to three months (Analysis 6.1). In the two studies from Venezuela (Cáceres García 2008 VEN; Gabaldon 1959 VEN), parasitaemia incidence returned briefly back to baseline levels, before the incidence again fell compared to baseline levels. These data are impossible to interpret without a control group.

Comparison 6.2: MDA plus vector control vs no MDA

Uncontrolled before-and-after studies: Two studies (Garfield 1983 NIC; Simeons 1938 IND) described the effect of MDA plus vector control measures on parasitaemia incidence during administration, with baseline monthly incidence levels ranging from 0.4/1000 to 156/1000. During MDA, the effects appear mixed, with an increase in incidence in one study and a decrease in the other (Analysis 6.2). These observations are probably seasonal and again highlight the difficulty of interpreting uncontrolled trials. At later time points, the incidence of malaria appears substantially reduced compared to baseline levels for up to a year (Analysis 6.2).

Both studies reported implementing larval control methods, which involved either oiling (Simeons 1938 IND) or larviciding based on large scale application of temephos to peridomestic breeding sites targeting *Aedes aegypti* (Garfield 1983 NIC).

Section 4: MDA of regimens containing 8-aminoquinolines versus regimens that do not

We found no studies directly comparing MDA regimens that included 8-aminoquinolines with regimens that did not.

We have instead attempted to compare these regimens indirectly through a subgroup analysis. This was not possible for studies conducted in settings of low endemicity due to their low number. The single cluster-randomized trial gave primaquine along with artesunate plus sulphadoxine-pyrimethamine but reported no episodes of parasitaemia or gametocytaemia at baseline or during follow-up (Shekalaghe 2011 TZA), and the single uncontrolled before-and-after study gave chloroquine alone (Malaria_Taiwan 1991 TWN).

Comparison 7: MDA vs no MDA; settings of moderate and high endemicity; subgrouped by inclusion of 8-aminoquinolines

Parasitaemia prevalence

Non-randomized controlled trials:

None of the non-randomized controlled studies from moderate endemic settings administered primaquine as part of MDA. Of the three studies from high endemic settings, two administered primaquine as part of MDA (Escudie 1962 BFA; Schneider 1961 BFA) and one did not (Molineaux 1980 NGA). During multiple MDA rounds, there was a substantial reduction in parasitaemia prevalence regardless of the presence or absence of primaquine, with no statistically significant differences between subgroups (test for subgroup differences $P = 0.57$, Analysis 7.1). At one to three months, the two studies without primaquine (Jones 1958 KEN; Roberts 1964 KEN) showed a larger impact than studies that included primaquine (Escudie 1962 BFA; Schneider 1961 BFA) (Analysis 7.2).

Uncontrolled before-and-after studies: Four studies reporting parasitaemia prevalence administered an 8-aminoquinoline as part of their MDA regimen (Kligler 1931 PSE: plasmochine 30 mg; Comer 1971 PAN: primaquine 40 mg; Hii 1987 MYS: primaquine 30 mg; Song 2010 KHM: primaquine 9 mg every 10 days). During MDA administration, there was no difference in impact between studies that administered primaquine and those that had not (test for subgroup differences $P = 0.08$, Analysis 7.3). Within the first month post-MDA, there was a substantial reduction in parasite prevalence in all four studies regardless of whether primaquine was given or not (test for subgroup differences $P = 0.12$, Analysis 7.4). At one to three months post-treatment, uncontrolled before-and-after studies that did not include an 8-aminoquinoline experienced greater reductions in parasitaemia prevalence compared to the one study that did use an 8-aminoquinoline as part of MDA (test for subgroup differences < 0.001 , Analysis 7.5). At four to six months post-MDA, there was no difference in impact between studies that administered primaquine and those that had not (test for subgroup differences $P = 0.07$, Analysis 7.6).

Section 5: MDA for different plasmodium species

Two non-randomized controlled studies (Jones 1958 KEN; Kaneko 2000 VUT) and five uncontrolled before-and-after studies (Malaria_Taiwan 1991 TWN; Metselaar 1961 PNG; Paik 1974a SLB; Song 2010 KHM; van Dijk 1961 PNG) report the effects of MDA on the prevalence of both *P. falciparum* and *P. vivax* parasitaemia. Among these, two studies compared MDA plus vector control with no intervention (Kaneko 2000 VUT; Paik 1974a SLB); the remaining studies compared MDA with no intervention.

Comparison 8: Subgrouped by plasmodium species

Non-randomized controlled studies: At baseline, there was a substantial imbalance in the prevalence of *P. vivax* parasitaemia, which would tend to underestimate the effect of MDA on *P. vivax* (Analysis 8.1). These two studies administered MDA as either pyrimethamine every six months for three rounds (Jones 1958 KEN) or as weekly doses of chloroquine, sulphadoxine-pyrimethamine and primaquine for nine weeks (Kaneko 2000 VUT); both produced mixed results. Kaneko 2000 VUT reported sustained impact on parasitaemia prevalence over several years of follow-up with no falciparum infections and few vivax cases, showing that the impact of MDA was larger for *P. falciparum*. Jones 1958 KEN also found a larger reduction in *P. falciparum* than *P. vivax* for up to about four months (Analysis 8.3; Analysis 8.4; Analysis 8.5).

Uncontrolled before-and-after studies: Four studies demonstrated a reduction in the prevalence of *P. vivax* parasitaemia during the first month post-MDA, although this was of a smaller magnitude than seen for *P. falciparum* (Analysis 8.3). These studies administered artesunate-piperazine plus primaquine (Song 2010 KHM), chloroquine plus pyrimethamine (Paik 1974a SLB) or chloroquine alone (Malaria_Taiwan 1991 TWN; van Dijk 1961 PNG). After one to three months of follow-up, the impact of MDA on parasitaemia prevalence for *P. vivax* was smaller than for *P. falciparum* (Analysis 8.4). By five months of follow-up, Paik 1974a SLB described greater reductions in parasitaemia prevalence for *P. vivax* infections compared to *P. falciparum* cases. In contrast, two studies from Asia (Malaria_Taiwan 1991 TWN; Song 2010 KHM) demonstrated larger reductions in parasitaemia prevalence for *P. falciparum* at six months (Song 2010 KHM) and after more than 12 months post-MDA (Malaria_Taiwan 1991 TWN; Song 2010 KHM).

Section 6: Adverse Events

Ten studies reported on adverse events (Archibald 1960 NGA; Comer 1971 PAN; Garfield 1983 NIC; Kaneko 2000 VUT; Kligler 1931 PSE; Najera 1973 NGA; Shekalaghe 2011 TZA; Simeons 1938 IND; Song 2010 KHM; von Seidlein 2003 GMB). Of these, only four studies conducted some level of active adverse event surveillance (Kligler 1931 PSE; Najera 1973 NGA; Shekalaghe 2011 TZA; von Seidlein 2003 GMB).

Kligler 1931 PSE and Song 2010 KHM reported no adverse events.

Minor side effects were reported in three studies (Archibald 1960 NGA; Najera 1973 NGA; von Seidlein 2003 GMB). Two studies conducting MDA with chloroquine plus pyrimethamine (Archibald 1960 NGA; Najera 1973 NGA) reported a number of children vomiting the drug. Complaints of dizziness, fever, diarrhoea, vomiting and itching within two days of taking sulphadoxine-pyrimethamine and artesunate were reported in von Seidlein 2003 GMB.

Five of the studies (Comer 1971 PAN; Garfield 1983 NIC; Kaneko 2000 VUT; Shekalaghe 2011 TZA; Simeons 1938 IND) reporting adverse events included an 8-aminoquinoline drug. Comer 1971 PAN described complaints of headache and nausea that were ascribed to pyrimethamine plus primaquine. In Kaneko 2000 VUT, some villagers reported vomiting after taking the tablets (chloroquine and primaquine and sulphadoxine-pyrimethamine). Common side effects described by Garfield 1983 NIC, which administered chloroquine and primaquine to all persons, included dizziness, nausea, vomiting and diarrhoea. In addition, Garfield 1983 NIC also reported occasional cases of psychomotor disturbance, temporary psychological abnormalities and haemolysis. One study (Shekalaghe 2011 TZA) reported a severe skin reaction one week after MDA with sulphadoxine-pyrimethamine plus artesunate plus primaquine. This study also reported several cases of moderate anaemia among glucose-6-phosphate dehydrogenase (G6PD) deficient participants given primaquine and one case of severe anaemia. Simeons 1938 IND conducted MDA with atebriin intramuscular and plasmochin simplex and reported four cases of haemoglobinuria, a known toxicity of 8-aminoquinoline drugs. Of those, two cases were fatal; the remaining two cases were mild. Additionally, abscesses were reported in 49 cases, while accounts of 'giddiness' were associated with the drug atebriin.

DISCUSSION

The main findings of this review, alongside assessments of the quality of evidence for each outcome using the GRADE approach, are summarized in three summary of findings tables: Table 6; Table 7; Table 8

Summary of main results

Two cluster-randomized trials, eight non-randomized controlled studies and 22 uncontrolled before-and-after studies are included in this review. The studies used a wide variety of MDA regimens incorporating different drugs, dosages, timings and numbers of MDA rounds. Many of the studies are now more than 30 years old.

Areas of low endemicity ($\leq 5\%$)

Within the first month post-MDA, a single uncontrolled before-and-after study conducted in 1955 on a small Taiwanese island reported a much lower prevalence of parasitaemia following a single course of chloroquine compared to baseline (*very low quality evidence*). This lower parasite prevalence was still present after more than 12 months (*very low quality evidence*) (see Table 6).

Areas of moderate endemicity (6% to 39%)

Within the first month post-MDA, the prevalence of parasitaemia was much lower in three non-randomized controlled studies from Kenya and India in the 1950s (*moderate quality evidence*) and in three uncontrolled before-and-after studies conducted between 1954 and 1961 (*low quality evidence*). The longest follow-up in these settings was four to six months. At this time point, the prevalence of parasitaemia remained substantially lower than controls in the two non-randomized controlled studies (*low quality evidence*). In contrast, the two uncontrolled before-and-after studies found mixed results: one found no difference and one found a substantially higher prevalence compared to baseline (*very low quality evidence*) (see Table 7).

Areas of high endemicity ($\geq 40\%$)

Within the first month post-MDA, the single cluster-randomized trial from the Gambia in 1999 found no difference in parasite prevalence (*low quality evidence*). However, prevalence was much lower during the MDA programmes in three non-randomized controlled studies conducted in the 1960s and 1970s (*moderate quality evidence*), and within one month of MDA in four uncontrolled before-and-after studies, including one study from Cambodia in 2006 (*low quality evidence*). Four trials reported changes in prevalence beyond three months. In the Gambia, the single cluster-randomized trial found no difference at five months (*moderate quality evidence*). The three uncontrolled before-and-after studies had mixed findings with large studies from Palestine and Cambodia showing sustained reductions at four months and 12 months, respectively, and a small study from Malaysia showing no difference after four to six months of follow-up (*low quality evidence*) (see Table 8).

MDA + vector control

In general, studies that included a vector control measure showed a large impact on parasitaemia and gametocytaemia prevalence both during MDA and up to three months post-intervention. In high-endemicity settings, one large study from Nigeria reported no difference after six months, whereas in moderate endemicity settings one study from an island of Vanuatu and one from the

highlands of Uganda noted sustained impact after more than 12 months.

8-aminoquinolines

We found no studies directly comparing MDA regimens that included 8-aminoquinolines with regimens that did not. In a crude subgroup analysis with a limited number of studies, we were unable to detect any evidence of additional benefit of primaquine in moderate- or high-transmission settings.

P. falciparum vs *P. vivax*

Reviewing studies that reported the impact of MDA on *P. falciparum* and *P. vivax* separately, most reported a larger impact on *P. falciparum* than *P. vivax* at all time intervals.

Adverse events

Adverse events were inadequately addressed in most studies. Notable severe drug reactions, including haemolysis, haemoglobinuria, severe anaemia and death, were reported for the co-administration of 8-aminoquinoline plus schizonticide, and severe skin reactions were documented with administration of sulphadoxine-pyrimethamine plus artesunate plus primaquine.

Overall completeness and applicability of evidence

The studies included in this review were conducted in a variety of settings in Africa, Asia, Europe and the Americas, and employed various designs, endemicities, drug regimens, co-intervention uses and numbers of rounds of MDA intervention. Comparative studies of malaria interventions are always confounded by differences in background epidemiology between diverse study areas, but, in this case, the situation is made even more difficult by the major differences in design between the studies. Therefore, the findings can be reasonably applied to scenarios that coincide closely with the aforementioned parameters but caution is advised in extrapolating results too broadly; the heterogeneity of the studies included in the overall analysis presents risks when trying to draw conclusions from pooled data. Furthermore, in reviewing these results, it is important to note the different properties of the antimalarials employed for mass treatment. Studies using non-gametocytocidal antimalarials should be interpreted separately from those using gametocytocidal antimalarials, so as to allow a fair comparison of pharmacodynamic properties. The same precautions should be taken when contrasting the impact of short-acting antimalarials such as the artemisinin derivatives with the impact of long-acting antimalarials such as sulphadoxine-pyrimethamine or piperazine-containing combinations.

Gaps remain in the research evidence and some of the evidence presented in this overview has serious limitations. Most studies do not explicitly describe the aims of the MDA programme (eg to interrupt transmission, to reduce transmission, to reduce morbidity from malaria, etc), making it difficult to determine whether studies were successful or not. Numerous studies also did not clearly indicate the timing of MDA in relation to the local transmission season. Too few studies were conducted in low transmission settings to determine the effect of MDA in these settings and the likely impact of this intervention in eliminating malaria. Furthermore, several outcome data included meta-analyses drawn from only one or two studies. There are exceptions to this, but even within this review the variability and high heterogeneity mean the

results may still be difficult to interpret. Under these circumstances, generalizing findings will remain a challenge.

Many of our pre-specified outcomes were not reported in all individual studies, although the majority of studies at least reported on parasitaemia and gametocytaemia prevalence. Few studies reported on parasitaemia incidence, anaemia prevalence or mortality, making it impossible to make any meaningful conclusions on these outcomes. Furthermore, some of the studies reporting on incidence presented data graphically, making it difficult for reviewers to extrapolate incidence estimates accurately without access to the raw data. Thus, these estimates may be imprecise and must be interpreted with caution.

Quality of the evidence

We assessed the quality of the evidence provided by the included studies using the GRADE approach, and have presented these results in the [Table 6](#), [Table 7](#) and [Table 8](#). The majority of the evidence in this review comes from non-randomized studies, which in most cases can provide only low or very low quality evidence. However, in some circumstances, very well conducted non-randomized studies can be upgraded to moderate or high quality evidence if they possess one or more of the following features: 1) a very large treatment effect; 2) evidence of a dose-response effect; 3) absence of plausible confounders that could be causing the effect.

Most MDA programmes are currently being planned for settings with low endemicity. However, studies of previous MDA programmes in these settings were assessed as providing only 'very low' quality evidence, meaning we cannot have any confidence in these results. The single study that provided any data on malaria prevalence in these settings was conducted in Taiwan in 1955 and is highly susceptible to confounding due to the lack of an adequate control group.

In settings with moderate endemicity, there is moderate quality evidence of substantial reductions in parasitaemia prevalence during the first month post-MDA. This evidence, from non-randomized controlled trials, was upgraded due to the consistently large effects seen and the supportive evidence from four uncontrolled before-and-after studies. Only two non-randomized controlled trials followed up beyond three months: one had baseline imbalances, which would lead to an overestimate of the observed effect, and both used MDA regimens that are not under consideration today (pyrimethamine). Consequently, despite the large effect seen, we graded this evidence as low quality.

The majority of studies of MDA have been conducted in high-transmission settings, where there is again moderate quality evidence from non-randomized controlled studies of large and consistent effects on parasitaemia prevalence during MDA programmes. However, only a single uncontrolled before-and-after study from Cambodia demonstrated effects lasting beyond three months post-intervention.

Potential biases in the review process

As with all reviews, there are risks of introducing bias at all stages in the review process. Several steps were taken in an attempt to reduce this bias. Throughout the review process, two authors independently assessed eligibility for inclusion of studies, and

carried out data extraction. Discrepancies were resolved by a third author. All foreign language papers were included.

Assessing the true impact of MDA programmes can be a challenge for many MDA studies, including those investigating simultaneous vector control efforts and lacking proper control groups. Furthermore, the impact of MDA on transmission is difficult to measure; most studies reported post-intervention effects for too short a time after the MDA to estimate adequately its impact on long-term transmission. Furthermore, the studies did not directly assess the potential of MDA to induce or promote drug resistance; however, a few studies ([Jones 1954 KEN](#); [Jones 1958 KEN](#); [Ricosse 1959 BFA](#)) did report on the development of drug resistance following the use of pyrimethamine monotherapy.

Agreements and disagreements with other studies or reviews

Antimalarial drug use for MDA has been reviewed previously ([Greenwood 2004](#); [von Seidlein 2003](#)). Thirteen of the studies in this current review ([Cavalié 1962 CMR](#); [De Zulueta 1961 UGA](#); [De Zulueta 1964 UGA](#); [Escudie 1962 BFA](#); [Garfield 1983 NIC](#); [Hii 1987 MYS](#); [Kaneko 2000 VUT](#); [Kondrashin 1985 IND](#); [Molineaux 1980 NGA](#); [Najera 1973 NGA](#); [Roberts 1964 KEN](#); [Singh 1953 IND](#); [von Seidlein 2003 GMB](#)) were also included in a review of MDA of antimalarial drugs published in 2003. However, several studies included in the [von Seidlein 2003](#) review were excluded from this review. The main reasons for exclusion were: 1) inadequate treatment doses ([Barber 1932](#); [Dola 1974](#); [MacCormack 1983](#); [Onori 1972](#); [Strangeways-Dixon 1950](#)); 2) individually randomized ([Doi 1989](#)); 3) insufficient information on outcomes of interest ([Yip 1998](#)); and 4) insufficient information on drug administration ([Baukapur 1984](#); [Lakshmanacharyulu 1968](#); [Sehgal 1968](#)).

In this review, we agree with the conclusion of [von Seidlein 2003](#) that MDA was generally unsuccessful in interrupting transmission but had a marked effect on parasite prevalence and on the incidence of clinical malaria in some cases. The [von Seidlein 2003](#) review also proposed a role for MDA in the control of epidemics and in the control of malaria in areas with a short transmission season, which this current review did not specifically address. Rather, this review used a systematic approach to demonstrate and quantify the differential impact of MDA on parasitaemia prevalence and incidence and on gametocytaemia prevalence depending on the timing of the post-MDA outcome measurement. Furthermore, this review assessed the addition of 8-aminoquinoline drugs into MDA regimens, as well as the differential impact of MDA on different plasmodium species (ie *P. falciparum* vs *P. vivax*), which no other review to date has attempted.

The findings of this review also appear to agree with other more recent modelling that suggests MDA could potentially eliminate transmission, and that the probability of this occurring goes up with lower baseline transmission, increased frequency of MDA and the addition of vector control measures ([Okell 2011](#)). Furthermore, the findings demonstrate that a single round of MDA will have only short-term effects in higher transmission settings. Theoretically, multiple rounds of optimally-timed MDA in a small, isolated community with low baseline transmission could eliminate malaria.

Another model using data from [Song 2010 KHM](#) demonstrated that in order to achieve malaria elimination a combination of

different strategies is required ([Maude 2012](#)). Specifically, MDA with artemisinin-piperaquine can significantly reduce parasite prevalence in the short term (< 1 year), especially multiple rounds during the low transmission season. The model predicted that the addition of primaquine might enhance the effect of artemisinin-based combination therapies in controlling or eliminating malaria, but this was not evident from this review. The addition of long-lasting ITNs further accelerated elimination efforts.

While this review does not completely reconcile the controversies that surround the use of MDA, it summarizes evidence showing that this strategy can reduce malaria burden and transmission in various settings. It also helps to identify gaps in the data and in our understanding of MDA, and can help to guide future antimalarial MDA interventions and their evaluation.

AUTHORS' CONCLUSIONS

Implications for practice

MDA of antimalarials using therapeutic doses has an immediate and short-term impact on parasitaemia prevalence and incidence and on gametocytaemia prevalence in all transmission settings. Although no cluster-randomized trial showed a sustained impact on these outcomes, a few non-randomized controlled studies and uncontrolled before-and-after studies did show sustained impact lasting beyond six months of follow-up. Studies with sustained impact were conducted in low or moderate transmission settings and on small islands or in highland areas. There is evidence that MDA produces larger reductions in parasitaemia prevalence for malaria caused by *P. falciparum* compared to *P. vivax*. The impact of adding an 8-aminoquinoline drug remains unclear, although no obvious benefit in moderate and high transmission areas was noted. No study directly compared MDA regimens that included an 8-aminoquinoline with regimens that did not. Several studies in this review that reported adverse events included an 8-aminoquinoline drug, with two studies reporting cases of haemolysis.

Still, the optimum transmission scenarios and drug intervention regimens for producing a sustained impact with MDA remain largely unknown. In addition, ensuring high coverage requires overcoming many logistical challenges; in order to achieve high levels of coverage, a target drug profile for MDA must be extremely safe, acceptable and efficacious. Even in settings with highly efficacious drugs, the overall field effectiveness of MDA will be greatly compromised if high coverage of the target population is not achieved.

Significant progress in malaria control has been made in several settings with an associated reduction in parasitaemia prevalence; however, with the limitations of currently available diagnostic tools, the elimination of all parasites may pose a challenge. MDA may be able to achieve the elimination of remaining parasite reservoirs among asymptomatic carriers. However, careful consideration should be given before attempting this approach, especially in light of increasing concern over the emergence and possible spread of artemisinin resistance by *falciparum* malaria. Geographically isolated areas (ie islands) where importation risk is lower and/or those with seasonal or lower transmission (ie highlands) may be more suited to MDA.

Implications for research

While most analyses demonstrate favourable short-term outcomes for MDA, additional high quality, cluster-randomized trials are required. These should have clearly defined objectives (eg to interrupt transmission, to reduce transmission or to impact malaria morbidity) and include participants of all age-groups. They also need to be conducted in a variety of transmission and seasonal settings with different epidemiological and socio-cultural determinants, in order to assess adequately the long-term impact of MDA on malaria transmission. Specifically, the deficiencies in design of many early studies have complicated the task of summarizing the effect of MDA on transmission. In addition, few studies have adequately assessed transmission endpoints. Rather, most studies use relatively standardized measures for parasitaemia prevalence or incidence. It remains unclear from current studies whether longer beneficial effects would be seen in settings of lower transmission. Studies that use a cluster-randomized design, with multiple rounds of MDA and a longer duration of follow up, are required for adequately assessing the nature of the effect of MDA on transmission. Furthermore, steps towards standardized approaches for measuring and reporting parasitaemia incidence, adverse events and other secondary outcomes would greatly improve comparability between studies.

The optimal number and interval timing of rounds of MDA also needs to be determined, as does the conditions under which MDA would yield the greatest benefit in terms of malaria endemicity and degree of other control measures. The design of the MDA

intervention needs to be adapted for its purpose during initial stages of malaria control programmes, in order to aim for large reductions in parasitaemia prevalence, or during latter stages to clear remaining infections. Also, although there are theoretical benefits to decreasing gametocyte carriage and thus transmission with the use of an 8-aminoquinoline, the actual benefits of adding it to a blood schizonticide, especially an ACT, need to be carefully studied. Lastly, resistance monitoring should be integrated into future MDA studies to understand better the impact of MDA on the development of drug resistance, especially if used in a setting of already failing drugs.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Archibald 1960 NGA

Methods	Dates of study: 1957-1959
	Location of study: Nigeria
	Malaria endemicity (prevalence): Intervention group 1 (Arugungu - June 1958): 28% in children 1-10 years; 29% in children 0-15 years [Moderate]. Intervention group 1 (Gulmare and Koei - October 1957): 64% in children 1-10 years; 58.3% in children 0-15 years [High].

Mass drug administration for malaria (Review)

Archibald 1960 NGA (Continued)

Transmission season: June to October

Malaria species: *P. falciparum*, *P. malariae*

Vector species: *A. gambiae*, *A. funestus*

Study design: Uncontrolled before-and-after study

Evaluation design: Cross-sectional surveys

Participants	Age groups included: All ages <u>Sample size</u> Intervention group 1 (mean): 10,000 Intervention group 2 (mean): 1300
Interventions	Intervention group 1 (Arugungu): MDA to all persons with chloroquine 600 mg and pyrimethamine 25 mg given monthly from June to October 1958. Coverage not specified. Co-intervention with IRS. Intervention group 2 (Gulmare and Koei): MDA to all persons with chloroquine 600 mg and pyrimethamine 25 mg given every six months (November 1957, May 1958, November 1958 and March 1959). Coverage not specified. Co-intervention with IRS.
Outcomes	Parasitaemia prevalence Gametocytaemia prevalence No adverse event surveillance conducted Adverse events reported: "There were substantial difficulties with toddlers taking chloroquine and a number of them vomited that drug."
Notes	MDA added to IRS programme. The outcomes for intervention groups 1 and 2 were assessed in a sub-sample of the treated population. A third intervention group received only pyrimethamine 25 mg but was not included in the meta-analysis due to reports of rapid development of resistance.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group

Mass drug administration for malaria (Review)

Archibald 1960 NGA (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	The highest number of confirmed absentees reported by the investigators in September 1958 in Argungu was only 625 (6%).
Selective reporting (reporting bias)	High risk	The number of children examined varied greatly between surveys without any explanation and a very small number of children were examined in Arugungu.
Other bias	High risk	Anecdotes of ill effects began to circulate and there was evidence of 'palming' of tablets.

Cavalie 1962 CMR

Methods	<p>Dates of study: 1960-1961</p> <p>Location of study: Cameroon</p> <p>Malaria endemicity (prevalence): Intervention group 1: 20% in children 2-9 years [Moderate]; 13% in all ages. Intervention group 2: 76% in children 2-9 years; 65% in all ages [High].</p> <p>Transmission season: May to June, November to December</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. malariae</i></p> <p>Vector species: <i>A. gambiae</i>, <i>A. funestus</i></p> <p>Study design: Uncontrolled before-and-after study</p> <p>Evaluation design: Cross-sectional surveys</p>
Participants	<p>Age groups included: Ages > 3 months</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): 22,500</p> <p>Intervention group 2 (mean): 7000</p>
Interventions	<p>Intervention group 1 (Secteur Sud): MDA administered to all persons aged > 3 months with chloroquine 600 mg and pyrimethamine 50 mg once for two rounds in July and November 1960. Coverage 76-92%. Co-intervention with IRS using DDT.</p> <p>Intervention group 2 (Secteur Nord): MDA administered to all persons aged > 3 months with chloroquine 600 mg and pyrimethamine 50 mg once for one round in November 1960. Coverage approximately 100%. Co-intervention with IRS using DDT.</p>
Outcomes	<p>Parasitaemia prevalence</p> <p>No adverse event surveillance conducted</p> <p>No adverse events reported</p>
Notes	<p>Data presented in Table XV was used in the meta-analysis. Parasitaemia prevalence results only presented for children > 3 months to 9 years of age; meta-analysis includes only first round data. Only 13 mixed infections of <i>P. falciparum</i> and <i>P. malariae</i> were found. The remaining were <i>P. falciparum</i> infections only.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
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Mass drug administration for malaria (Review)

Cavalie 1962 CMR (Continued)

Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement. No reasons for missing data provided.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Low risk	No other bias detected

Comer 1971 PAN

Methods	<p>Dates of study: 1965-1968</p> <p>Location of study: Panama</p> <p>Malaria endemicity (prevalence): 17.4% in all ages [Moderate]</p> <p>Transmission season: Rainy season late May to late December</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. vivax</i></p> <p>Vector species: Not specified</p> <p>Study design: Uncontrolled before-and-after study</p> <p>Evaluation design: Cross-sectional surveys</p>
Participants	<p>Age groups included: Ages > 6 months</p> <p><u>Sample size</u></p> <p>Intervention group 1 mean (range): 1709 (1548 - 1908)</p>
Interventions	<p>Intervention group 1 (Valle del Rio Sambu): MDA to all persons aged > 6 months with pyrimethamine 50 mg (cycles 1-25)/ 75 mg (cycles 26-49) and primaquine 40 mg given every 2 weeks for 2 years from August 1966 to April 1968. Coverage 61-87%. No co-interventions.</p>
Outcomes	<p>Parasitaemia prevalence</p>

Mass drug administration for malaria (Review)

Comer 1971 PAN (Continued)

No adverse event surveillance conducted

Adverse events reported: The acceptance of drugs by the population was excellent. Complaints of nausea and headache were reported, but no other serious side effects were described. None of the people who complained of headaches or nausea refused to take the medicine in subsequent cycles. The number of people who refused to take the medicine was < 1% of the population covered by the programme.

Notes No post-intervention data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Coupon system used to track patients; all persons included in the surveys.
Selective reporting (reporting bias)	Low risk	All intended outcomes reported
Other bias	Low risk	No other bias detected

Cáceres García 2008 VEN

Methods

Dates of study: 2002-2007

Location of study: Venezuela

Malaria endemicity (incidence): 22/1000 monthly incidence in all ages

Transmission season: November

Malaria species: *P. vivax*

Vector species: Not specified

Study design: Uncontrolled before-and-after study

Mass drug administration for malaria (Review)

Cáceres Garcia 2008 VEN (Continued)

Evaluation design: Passive surveillance

Participants	Age groups included: Ages > 6 months; non-pregnant <u>Sample size</u> Intervention group 1: 25,722
Interventions	Intervention group 1 (6 municipalities in Estado Sucre): MDA to all non-pregnant persons aged >6 months with chloroquine 25 mg/kg administered over 3 days and primaquine 3.5 mg/kg administered over 7 days in November 2002. Coverage 77% (of census)/ 86% (of included). No co-intervention specified.
Outcomes	Parasitaemia incidence No adverse event surveillance conducted No adverse events reported
Notes	MDA done in setting of an outbreak

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Passive surveillance of large municipalities after one round of treatment
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias detected

De Zulueta 1961 UGA

Methods Dates of study: 1959-1960

Mass drug administration for malaria (Review)

De Zulueta 1961 UGA (Continued)

Location of study: Uganda

Malaria endemicity (prevalence): 34% in children 2-9 years; 17% in all ages [Moderate]

Transmission season: Rainy season April to May, August to November

Malaria species: *P. falciparum*, *P. malariae*

Vector species: *A. gambiae*, *A. funestus*

Study design: Uncontrolled before-and-after study

Evaluation design: Cross-sectional surveys

Participants	Age groups included: All ages
	<u>Sample size</u>
	Intervention group 1 mean (range): 30,384 (10,303 - 59,605)
Interventions	Intervention group 1 (North Kigezi): MDA administered to all persons with chloroquine 600 mg and pyrimethamine 50 mg every three months for four rounds at the time of IRS application from May 1959 to May 1960. Coverage 80%. Co-intervention with IRS.
Outcomes	Parasitaemia prevalence
	Gametocytaemia prevalence
	No adverse event surveillance conducted
	No adverse events reported
Notes	Outcomes assessed in a sub-sample of the treated population.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Cooperation of the local inhabitants was remarkably good and not a single dwelling was left unsprayed

Mass drug administration for malaria (Review)

De Zulueta 1961 UGA (Continued)

Selective reporting (reporting bias)	Low risk	Increased number of samples from hyperendemic areas in the post-intervention survey
Other bias	Low risk	No other bias detected

De Zulueta 1964 UGA

Methods	<p>Dates of study: 1960</p> <p>Location of study: Uganda</p> <p>Malaria endemicity (prevalence): 23% in children 2-9 years; 21% in all ages [Moderate]</p> <p>Transmission season: Rainy season April to May, August to November</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. malariae</i></p> <p>Vector species: <i>A. gambiae</i></p> <p>Study design: Uncontrolled before-and-after study</p> <p>Evaluation design: Cross-sectional surveys</p>
Participants	<p>Age groups included: Ages > 3 months</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): 16,000</p>
Interventions	<p>Intervention group 1 (Lake Bunyonyi): MDA to all persons aged > 3 months with chloroquine 600 mg and pyrimethamine 50 mg once per round for two rounds (April to May 1960 and September to October 1960). Coverage approximately 50% in the first round. Co-intervention with IRS.</p>
Outcomes	<p>Parasitaemia prevalence</p> <p>No adverse event surveillance conducted</p> <p>No adverse events reported</p>
Notes	<p>Outcomes assessed in a sub-sample of the treated population. <i>A. funestus</i> disappeared after one year of spraying and no new malaria cases were noted two years later.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group

De Zulueta 1964 UGA (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail, but the total number surveyed differs greatly between surveys
Selective reporting (reporting bias)	Low risk	All relevant outcomes were measured
Other bias	High risk	Only about half of the population was given MDA during the first round

Escudie 1962 BFA

Methods	<p>Dates of study: 1960-1961</p> <p>Location of study: Burkina Faso</p> <p>Malaria endemicity (prevalence): Comparison group 1: 56.1% in children 0-10 years [High]</p> <p>Transmission season: June to December</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. ovale</i>, <i>P. malariae</i></p> <p>Vector species: <i>A. gambiae</i>, <i>A. funestus</i>, <i>A. nili</i></p> <p>Study design: Non-randomized controlled study</p> <p>Evaluation design: Cross-sectional surveys</p>
Participants	<p>Age group included: All ages</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): 1890</p> <p>Intervention group 2 (mean): 2560</p> <p>Intervention group 3 (mean): 5400</p> <p>Intervention group 4 (mean): 3490</p> <p>Comparison group 1 (mean): Not described</p> <p>Comparison group 2 (mean): Not described</p>
Interventions	<p>Intervention group 1: MDA to all persons with a single dose of either chloroquine-primaquine (600 mg/15 mg) or amodiaquine-primaquine (600 mg/15 mg) every 28 days from June to December 1960. Coverage 75.2 to 91.2%. No co-interventions.</p> <p>Intervention group 2: MDA to all persons with a single dose of either chloroquine-primaquine (600 mg/15 mg) or amodiaquine-primaquine (600 mg/15 mg) every 14 days from June to December 1960. Coverage 84.1 to 96.5%. No co-interventions.</p>

Escudie 1962 BFA (Continued)

Intervention group 3: MDA to all persons with a single dose of either chloroquine-primaquine (600 mg/15 mg) or amodiaquine-primaquine (600 mg/15 mg) every 28 days from June to December 1960. Coverage 80.9 to 91.8%. Co-intervention with IRS using DDT annually.

Intervention group 4: MDA to all persons with a single dose of either chloroquine-primaquine (600 mg/15 mg) or amodiaquine-primaquine (600 mg/15 mg) every 14 days from June to December 1960. Coverage 82.1 to 93.8%. Co-intervention with IRS using DDT annually.

Comparison group 1: Control villages. No co-interventions.

Comparison group 2: Villages sprayed with IRS using DDT annually. No other co-interventions.

Outcomes	Parasitaemia prevalence Gametocytaemia prevalence No adverse event surveillance conducted No adverse events reported
Notes	Outcomes assessed in a sub-sample of the treated population (children 0-10 years). Baseline data from June 1960 survey. Ninety percent of cases are <i>P. falciparum</i> infections; <i>P. ovale</i> is rare and <i>P. malariae</i> is very rare.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Assignment to MDA was not randomized although drug assignment was randomized
Allocation concealment (selection bias)	High risk	Non-randomized controlled study
Baseline imbalance (selection bias)	High risk	Baseline parasitaemia estimates are not balanced between the intervention groups and the comparison groups. Also, there was large variability in endemicity between comparison group 1 villages.
Contamination protection	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel aware of treatment, but unclear if this impacted outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not blinded, but unclear if this impacted outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adults included in MDA, but not in the evaluation. Only children 0-10 years of age were examined in the malaria surveys before, during and after MDA.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes of interest are reported
Other bias	Unclear risk	Atypical seasonal changes experienced in 1959-1960, but it is unclear if these changes impacted outcomes.

Gabalton 1959 VEN

Methods	Dates of study: 1956-1957 Location of study: Venezuela Malaria endemicity (incidence): 0.4/1000 baseline monthly incidence Transmission season: May to November Malaria species: <i>P. vivax</i> Vector species: <i>A. aquasalis</i> , <i>A. nuneztovari</i> Study design: Uncontrolled before-and-after study Evaluation design: Active and passive surveillance
Participants	Age groups included: Ages > 1 month <u>Sample size</u> Intervention group 1 (mean): 111,995
Interventions	Intervention group 1: Eastern Venezuela (174 localities, 3084 houses, 16,416 persons) and Western Venezuela (735 localities, 17,638 houses, 95,579 persons): MDA to all persons aged > 1 month with pyrimethamine 50 mg per week for 24 weeks from July 1957 to December 1957. Coverage not specified. Co-intervention with IRS.
Outcomes	Parasitaemia incidence No adverse event surveillance conducted No adverse events reported
Notes	MDA added to IRS program

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group

Gabaldon 1959 VEN (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All houses numbered. Envelope system for drug dispensers and slide collectors. Cooperation of the people was excellent. Active search for all infections and passive search at all medical dispensaries in the area.
Selective reporting (reporting bias)	Low risk	Most persons received more than 19 treatments; however, the actual figures are not reported due to "lack of mechanical tabulation of the data". The number of persons with relapses who had less than 19 treatments demonstrated similar trends to those who received 19 or more treatments.
Other bias	Low risk	No other bias detected

Garfield 1983 NIC

Methods	Dates of study: 1981-1982 Location of study: Nicaragua Malaria endemicity (incidence): 0.4/1000 baseline monthly incidence Transmission season: November to March Malaria species: <i>P. falciparum</i> , <i>P. vivax</i> Vector species: <i>A. albimanus</i> Study design: Uncontrolled before-and-after study Evaluation design: Passive surveillance
Participants	Age groups included: Ages > 1 year <u>Sample size</u> Intervention group 1 (mean): 2,300,000
Interventions	Intervention group 1: MDA administered to all persons aged > 1 year with chloroquine 1500 mg and primaquine 45 mg over three days given once to the entire population of Nicaragua in November 1981. Coverage 70-80%. Co-intervention with larviciding using large scale application of temephos to peridomiliary breeding sites targeting <i>Aedes aegypti</i> , but likely to have an effect on anophelines.
Outcomes	Parasitaemia incidence No adverse event surveillance conducted Adverse events reported: Common side effects included dizziness, nausea, vomiting and diarrhoea. Occasional cases of psychomotor disturbance, temporary psychological abnormalities and haemolysis.
Notes	Data used in the meta-analysis was extrapolated from graphs presented in the text; baseline MDA estimates were determined using monthly surveillance data from 1974-1981.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group

Garfield 1983 NIC (Continued)

Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Single treatment episode after conducting a census, door-to-door education and promotion of community participation.
Selective reporting (reporting bias)	Low risk	National passive surveillance
Other bias	Low risk	No other bias detected

Gaud 1953 MAR

Methods	Dates of study: 1952 Location of study: Morocco Malaria endemicity (prevalence): 41.5% in all ages (baseline) [High] Transmission season: June to October Malaria species: <i>P. falciparum</i> , <i>P. vivax</i> Vector species: Not specified Study design: Uncontrolled before-and-after study Evaluation design: Cross-sectional surveys
Participants	Age groups included: All ages <u>Sample size:</u> Intervention group 1 (mean): 3000
Interventions	Intervention group 1: MDA administered to all persons with amodiaquine 600 mg given once in the summer of 1952. Coverage not specified. No co-interventions.
Outcomes	Parasitaemia prevalence No adverse event surveillance conducted No adverse events reported

Mass drug administration for malaria (Review)

Gaud 1953 MAR (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Low risk	No other bias detected

Hii 1987 MYS

Methods	<p>Dates of study: 1984-1985</p> <p>Location of study: Malaysia</p> <p>Malaria endemicity (prevalence): Intervention group 1 (December 1984 baseline survey): 46.3% in children 0-8 years [High]; Intervention group 2 (December 1984 baseline survey): 55.6% in children 0-8 years [High]</p> <p>Transmission season: Perennial</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. malariae</i>, <i>P. vivax</i></p> <p>Vector species: <i>A. balabacensis</i></p> <p>Study design: Uncontrolled before-and-after study</p> <p>Evaluation design: Cross-sectional surveys and active surveillance</p>
Participants	<p>Age groups included: All ages</p> <p><u>Sample size</u></p>

Mass drug administration for malaria (Review)

Hii 1987 MYS (Continued)

Intervention group 1 (mean): 754

Intervention group 2 (mean): 148

Interventions	<p>Intervention group 1: MDA administered to all persons (139 households in five villages) with sulfadoxine-pyrimethamine (1500 mg/75 mg) and primaquine 30 mg once in December 1984 to January 1985. Coverage 87%. Co-intervention with permethrin-impregnated bed nets to all households.</p> <p>Intervention group 2: MDA administered to all persons (nine households in one village) with sulfadoxine-pyrimethamine (1500 mg/75 mg) and primaquine 30 mg once in December 1984 to January 1985. Coverage 76%. No co-interventions.</p>
Outcomes	<p>Parasitaemia prevalence</p> <p>Parasitaemia incidence</p> <p>Gametocyaemia prevalence</p> <p>No adverse event surveillance conducted</p> <p>No adverse events reported</p>
Notes	<p>Though the entire population was treated, thick and thin blood films were collected during eight surveys on a population of 286 children aged 0-8 years. Only data for these children were reported and therefore used in the meta-analysis. Furthermore, because the study design included a comparison group that received MDA, the intervention and comparison groups will be treated as two intervention groups and each intervention group will be analyzed in the meta-analysis as a separate uncontrolled before-and-after study. Lastly, due to insufficient information to extract incidence data, parasitaemia incidence was not included as an outcome in the meta-analysis.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	High risk	Though the entire population was treated, thick and thin blood films were collected during eight surveys on a population of 286 children aged 0-8 years. Only 29.7% of children were present at every one of the eight sessions.
Selective reporting (reporting bias)	High risk	The study report fails to include results on <i>P. vivax</i> infections that would be expected to have been reported for such a study. The study methods indicate

Hii 1987 MYS (Continued)

that thick blood films will be classified as "positive or negative for asexual and/or sexual parasites of either *P. falciparum*, *P. vivax*, *P. malariae*, or mixed infections". Only parasitological findings for *P. falciparum* are described and presented in detail.

Other bias	Low risk	With the exception of two study villages, which are both intervention group 1 sites, the study villages are "well separated and demarcated". Therefore, it is unlikely that contamination between sites occurred. All villages also received the same treatment dose and schedule. However, it should be noted that in the meta-analysis, the two interventions were analyzed as two separate uncontrolled before-and-after studies.
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Houel 1954 MAR

Methods	Dates of study: 1953 Location of study: Morocco Malaria endemicity (prevalence): 14.3%, children only (August 1953 baseline survey) [Moderate] Transmission season: July to November Malaria species: <i>P. falciparum</i> , <i>P. malariae</i> , <i>P. vivax</i> Vector species: Not specified Study design: Uncontrolled before-and-after study Evaluation design: Cross-sectional surveys
Participants	Age groups included: All ages <u>Sample size</u> Intervention group 1 (mean): 9999
Interventions	Intervention group 1: MDA administered to all persons with pyrimethamine 100 mg once in June 1953 to September 1953. Coverage not specified. Co-intervention with IRS prior to MDA.
Outcomes	Parasitaemia prevalence Gametocytaemia prevalence No adverse event surveillance conducted No adverse events reported
Notes	Only results from the 147 children examined were included in the meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group

Houel 1954 MAR (Continued)

Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	High risk	While adults were included in MDA, only a subset of children were included in the evaluation.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	No data on coverage of intervention

Jones 1954 KEN

Methods	<p>Dates of study: 1952-1953</p> <p>Location of study: Kenya</p> <p>Malaria endemicity (prevalence): 34.8% (baseline survey in a random sample of adults and infants); 32.6% (baseline survey in school children) [Moderate]</p> <p>Transmission season: January to March, May to August</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. malariae</i></p> <p>Vector species: <i>A. gambiae</i>, <i>A. funestus</i></p> <p>Study design: Uncontrolled before-and-after study</p> <p>Evaluation design: Cross-sectional surveys</p>
Participants	<p>Age groups included: All ages</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): 3721 (including 297 school children)</p>
Interventions	<p>Intervention group 1: MDA administered to all persons in Makueni with pyrimethamine 100 mg once for three rounds in September 1952, March 1953 and September 1953. Coverage not specified. No co-interventions.</p>
Outcomes	<p>Parasitaemia prevalence</p> <p>No adverse event surveillance conducted</p> <p>No adverse events reported</p>

Jones 1954 KEN (Continued)

Notes Following the first MDA round, blood smears were taken from random samples of the adult and infant (< 5 years) population and from all school children for a year. Due to the high degree of resistance that developed following two MDA rounds, parasitaemia prevalence results in the meta-analysis reflect only first round MDA results for infants and adults.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual data kept of all school children and of all subjects with malaria attending the dispensary
Selective reporting (reporting bias)	Low risk	Blood smears collected from random samples of adults and infants and of all school children monthly for a year following the first MDA round. All pre-specified outcomes have been reported.
Other bias	High risk	Complicated by resistance

Jones 1958 KEN

Methods

Dates of study: 1952-1953

Location of study: Kenya

Malaria endemicity (prevalence): Intervention group 1 (September 1952): 60% in school-age children; Comparison group 1 (September 1953): 34% in school-age children [Moderate]

Transmission season: January to March, May to August

Malaria species: *P. falciparum*, *P. malariae*, *P. vivax*

Vector species: *A. gambiae*, *A. funestus*

Study design: Non-randomized controlled study

Evaluation design: Cross-sectional surveys

Jones 1958 KEN (Continued)

Participants	Age groups included: All ages; school-age children <u>Sample size</u> Intervention group 1 (range): 3721-4500 Comparison group 1: Not specified
Interventions	Intervention group 1: MDA administered to all school children in Makueni with pyrimethamine 100 mg for three rounds in September 1952, March 1953 and September 1953. Coverage not specified. No co-interventions. Comparison group 1: School children in Okia used as a comparison arm. No co-interventions.
Outcomes	Parasitaemia prevalence Gametocytaemia prevalence No adverse event surveillance conducted No adverse events reported
Notes	Outcome data for the intervention group is a subset of the Jones 1954 KEN study. The meta-analysis only included first-round results. Gametocytaemia prevalence data is for <i>P. falciparum</i> only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomized controlled study
Allocation concealment (selection bias)	High risk	Non-randomized controlled study
Baseline imbalance (selection bias)	High risk	Baseline parasitaemia estimates are not balanced between the intervention group and the comparison group.
Contamination protection	Unclear risk	Although the comparison group site was 13 miles from the intervention group site, there is no indication whether the control group was adequately protected against contamination. It is quite possible that the control group received the intervention.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants and personnel aware of treatment, but unclear if this impacted outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not blinded, but unclear if this impacted outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Individual data kept of all school-age children and of all subjects with malaria attending the dispensary. No antimalarials were sold in local shops. At the end of the 12th month of evaluation, 221 children remained out of the original 297 children.
Selective reporting (reporting bias)	Low risk	Blood smears from random samples and all school-age children. Over the course of the study, the school population rose by 178 children. To avoid confusion, the investigators excluded these additional children from the figures

Mass drug administration for malaria (Review)

Jones 1958 KEN (Continued)

used to compile prevalence and only reported data from the original 297 children.

Other bias	High risk	Complicated by drug resistance
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Kaneko 2000 VUT

Methods	<p>Dates of study: 1991-1999</p> <p>Location of study: Vanuatu</p> <p>Malaria endemicity (prevalence): Intervention group 1 (January - September 1991): 15.7% in all ages; Comparison group 1 (May 1990): 28.8% in all ages [Moderate].</p> <p>Transmission season: December to April</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. vivax</i></p> <p>Vector species: <i>A. farauti</i></p> <p>Study design: Non-randomized controlled study</p> <p>Evaluation design: Cross-sectional surveys</p>
Participants	<p>Age groups included: All ages</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): 718</p> <p>Comparison group 1 (mean): 19,289</p>
Interventions	<p>Intervention group 1: MDA administered to all persons in Aneityum weekly for nine weeks with chloroquine 600 mg and sulfadoxine-pyrimethamine 1500 mg/75 mg and primaquine 45 mg once a week in weeks 1, 5, and 9; chloroquine 300 mg and primaquine 45 mg once a week in weeks 2, 3, 4, 6, 7, and 8 in September 1991 to November 1991. Coverage 79 to 92%. Co-intervention with larvivorous fish in several identified breeding sites and universal coverage with insecticide treated bed nets (about 0.94 nets per villager).</p> <p>Comparison group 1: Persons living in Malakula Island. Co-intervention with bed nets (approximately 20% coverage).</p>
Outcomes	<p>Parasitaemia prevalence</p> <p>No adverse event surveillance conducted</p> <p>Adverse events reported: Some villagers reported vomiting after taking the tablets.</p>
Notes	<p>Another village on Futana island was included in the study for comparison; however, because no parasitaemia was detected in the two surveys on Futuna, it was excluded from the meta-analysis. The meta-analysis only included data from Aneityum for the months of January and September 1991 (before MDA) and March 1998 (post-MDA).</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomized controlled study

Kaneko 2000 VUT (Continued)

Allocation concealment (selection bias)	High risk	Non-randomized controlled study
Baseline imbalance (selection bias)	Low risk	According to investigators, "the parasite rates were initially similar on Aneityum and Malakula islands and in general, decreased with age".
Contamination protection	Low risk	The comparison group was a village from Malakula, an adjacent island; therefore, it is unlikely that the comparison group received the intervention.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not blinded, but unclear if this impacted outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not blinded, but unclear if this impacted outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 7.9% of doses unable to be administered and only 3.8% doses were not properly reported and could not be confirmed. The overall calculated compliance rate of the remaining doses was 88.3%.
Selective reporting (reporting bias)	High risk	Of the 13 surveys, two covered only school children whereas the other 11 surveys covered the entire population of Aneityum.
Other bias	Low risk	No other bias detected

Kligler 1931 PSE

Methods	<p>Dates of study: 1930</p> <p>Location of study: Palestine (known as British Mandate Palestine at the time of the study's publication)</p> <p>Malaria endemicity (prevalence): 35% in all ages; 67% in children 2-10 years [High]</p> <p>Transmission season: October to December</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. malariae</i>, <i>P. vivax</i></p> <p>Vector species: <i>A. elutus</i></p> <p>Study design: Uncontrolled before-and-after study</p> <p>Evaluation design: Cross-sectional surveys and active surveillance</p>
Participants	<p>Age groups included: All ages</p> <p><u>Sample size</u></p> <p>Intervention group 1 mean (range): 953 (899-993)</p>
Interventions	<p>Intervention group 1: MDA administered to all persons in five selected villages with plasmochine 30 mg plus quinine 900 mg twice daily for five days every three weeks for three rounds between September and November 1930. Coverage 78.8%. No co-interventions.</p>
Outcomes	<p>Parasitaemia prevalence</p> <p>Gametocyaemia prevalence</p>

Mass drug administration for malaria (Review)

Kligler 1931 PSE (Continued)

Adverse event surveillance conducted (active during the course of the treatment)

Adverse events reported: No ill results were noted during the entire course of treatment.

Notes

Noted that repeated treatments tended to increase resistance.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	High risk	There was a large drop in the number of villages surveyed from baseline to post-survey without any explanation.
Selective reporting (reporting bias)	High risk	Five villages were treated but only select villages reported outcome data.
Other bias	Low risk	No other bias detected

Kondrashin 1985 IND

Methods

Dates of study: 1981

Location of study: India

Malaria endemicity (incidence): 4/1000 baseline monthly incidence

Transmission season; April to August

 Malaria species: *P. falciparum*, *P. vivax*

Vector species: Not specified

Study design: Uncontrolled before-and-after study

Evaluation design: Passive surveillance

Participants

Age groups included: All ages

Mass drug administration for malaria (Review)

Kondrashin 1985 IND (Continued)

Sample size

Intervention group 1 (mean): 51,325

Interventions	Intervention group 1: MDA administered to all persons with chloroquine 600 mg (plus primaquine 45 mg in falciparum areas only) for one round in March to May 1981 in four primary health centres and two rounds in February to March 1981 and June to September 1981 in four other primary health centres. Coverage 85%. Co-intervention with IRS.
Outcomes	Parasitaemia incidence No adverse event surveillance conducted No adverse events reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 or 2 rounds of treatment with 85% coverage
Selective reporting (reporting bias)	Unclear risk	No mention of the thoroughness of passive surveillance
Other bias	High risk	A likely increase in <i>P. falciparum</i> due to labour movement into treated area

Malaria_Taiwan 1991 TWN

Methods	Dates of study: 1955 Location of study: Taiwan
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Malaria_Taiwan 1991 TWN (Continued)

Malaria endemicity (prevalence): 4.12% in all ages (May 1955 survey); 2.93% in all ages (November 1955) [Low]

Transmission season: Not described

Malaria species: *P. falciparum*, *P. malariae*, *P. vivax*

Vector species: *A. maculatus*, *A. minimus*, *A. sinensis*

Study design: Uncontrolled before-and-after study

Evaluation design: Cross-sectional surveys and passive surveillance

Participants	Age groups included: All ages, except infants <u>Sample size</u> Intervention group 1 mean (range): 1520 (1502-1537)
Interventions	Intervention group 1: MDA administered to all persons, except infants, in Lanyu with a single dose of chloroquine (12 mg/kg) in November 1955. Coverage not specified. Co-intervention with IRS using DDT.
Outcomes	Parasitaemia prevalence No adverse event surveillance conducted No adverse events reported
Notes	Post-MDA (> 12 months) estimated using survey data from April-May 1957 and April 1960

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement
Selective reporting (reporting bias)	Low risk	The first three malariometric baseline surveys reported consisted of only a portion of the entire population on the island. Subsequent surveys examined all inhabitants. While these disproportionate samples could result in a certain

Mass drug administration for malaria (Review)

Malaria_Taiwan 1991 TWN (Continued)

bias when compared to the remaining surveys that comprised the entire population, the investigators weighted the first three surveys according to the natural distribution of the population.

Other bias	Low risk	No other bias detected
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Metselaar 1961 PNG

Methods	<p>Dates of study: 1958-1959</p> <p>Location of study: Papua New Guinea</p> <p>Malaria endemicity (prevalence): 46-80% in children 2-11 years; 46% in all ages before spraying [High]; During spraying 13-21% in children 2-11 years; 12% in all ages [Moderate]</p> <p>Transmission season: Not described</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. malariae</i>, <i>P. vivax</i></p> <p>Vector species: <i>A. punctulatus</i>, <i>A. farauti</i>, <i>A. koliensis</i></p> <p>Study design: Uncontrolled before-and-after study</p> <p>Evaluation design: Cross-sectional surveys</p>
Participants	<p>Age groups included: All ages</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): 2500</p>
Interventions	<p>Intervention group 1 (Sentani): MDA administered to all persons in sprayed areas with chloroquine 450 mg plus pyrimethamine 50 mg at weekly intervals for five rounds in 1958 and for one round in 1959. Two villages with high absolute parasite rates received an additional round of treatment in 1959. In addition, during all rounds, positives received chloroquine for an additional three successive days, completing a full course (1350 mg base for adults). Coverage 90%. Co-intervention with IRS.</p>
Outcomes	<p>Parasite prevalence</p> <p>No adverse event surveillance conducted</p> <p>No adverse events reported</p>
Notes	<p>Baseline data from 1958 survey</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group

Mass drug administration for malaria (Review)

Metselaar 1961 PNG (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Low risk	90% coverage, but no further description
Selective reporting (reporting bias)	Unclear risk	Selection for inclusion in surveys not described
Other bias	Low risk	No other bias detected

Molineaux 1980 NGA

Methods	<p>Dates of study: 1970-1975</p> <p>Location of study: Nigeria</p> <p>Malaria endemicity (prevalence): 46% in all ages [High]</p> <p>Transmission season: April to October</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. malariae</i>, <i>P. ovale</i></p> <p>Vector species: <i>A. gambiae</i>, <i>A. funestus</i></p> <p>Study design: Non-randomized controlled study</p> <p>Evaluation design: Cross-sectional surveys and active surveillance</p>
Participants	<p>Age groups included: All ages, but infants not included in MDA until their first malaria episode.</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): 14,129</p> <p>Intervention group 2 (mean): 1810</p> <p>Comparison group 1 (mean): 32,828</p> <p>Comparison group 2 (mean): ND</p>
Interventions	<p>Intervention group 1 (Low frequency MDA+IRS group): MDA administered to all ages, except for infants who have not had their first malaria episode, with sulfalene-pyrimethamine 500 mg/25 mg every 10 weeks from April 1972 to October 1973. Coverage 85%. Co-intervention with IRS using propoxur 3-4 rounds per year.</p> <p>Intervention group 2 (High frequency MDA+IRS group): MDA administered to all ages, except for infants who have not had their first malaria episode, with sulfalene-pyrimethamine 500 mg/25 mg every two weeks during the wet season and every 10 weeks during the dry season from April 1972 to October 1973. Coverage 85%. Co-intervention with IRS using propoxur 3-4 rounds per year.</p> <p>Comparison group 1: IRS using propoxur 3-4 rounds per year.</p>

Mass drug administration for malaria (Review)

Molineaux 1980 NGA (Continued)

Comparison group 2: No interventions.

Outcomes	Parasitaemia prevalence
	Gametocytaemia prevalence
	Mortality
	No adverse event surveillance conducted
	No adverse events reported

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomized controlled study
Allocation concealment (selection bias)	High risk	Non-randomized controlled study
Baseline imbalance (selection bias)	Low risk	Similar malaria characteristics between groups
Contamination protection	Low risk	It was desirable to allocate contiguous areas to the same treatment and also to reduce the effect of migrations by having similarly treated buffer zones around the evaluation villages.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned but unclear if this impacted outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent reexamination of slides
Incomplete outcome data (attrition bias) All outcomes	Low risk	Operation aimed for total coverage
Selective reporting (reporting bias)	Low risk	The surveys covered the total <i>de facto</i> population of selected village clusters and all possible outcomes measured and reported.
Other bias	Low risk	No other bias detected

Najera 1973 NGA

Methods	Dates of study: 1966-1968
	Location of study: Nigeria
	Malaria endemicity (prevalence): Comparison group 1: 28.9% in all ages [Moderate]
	Transmission season: May to September

Mass drug administration for malaria (Review)

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Najera 1973 NGA (Continued)

 Malaria species: *P. falciparum*

 Vector species: *A. gambiae*, *A. funestus*

Study design: Non-randomized controlled study (no post-intervention measurements)

Evaluation design: Cross-sectional surveys

Participants	Age groups included: Ages > 3 months <u>Sample size</u> Intervention 1 mean (range): 52,000 (52,060 to 53,897) Comparison 1 mean: 11,500
Interventions	Intervention group 1: MDA administered to all persons aged > 3 months with chloroquine 450 mg and pyrimethamine 45 mg every 60 days for 11 rounds from November 1966 to August 1968. Coverage 78 to 92%. Co-intervention with IRS. Comparison group 1: Co-intervention with IRS only. Coverage not described.
Outcomes	Parasitaemia prevalence Gametocytaemia prevalence Active adverse event surveillance conducted Adverse events reported: Direct observation of 5003 treatments during MDA rounds 9 and 10 revealed 2% vomiting immediately after taking the drug. When a subset of the population was asked about vomiting, 9% reported this symptom.
Notes	Data collected during rounds 2 to 11 are summarized as during MDA results. This is problematic as the initial decline and later rise of cases during the two years of drug administration is aggregated. Evaluation conducted in a subset of treated population.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomized controlled study
Allocation concealment (selection bias)	High risk	Non-randomized controlled study
Baseline imbalance (selection bias)	High risk	The comparison area was not comparable to the intervention area in terms of entomologic or parasitological parameters.
Contamination protection	Low risk	Treated large peripheral zone, but evaluation done in central zone only
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not blinded, but unclear if this impacted outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned, but unclear if this impacted outcomes

Najera 1973 NGA (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Recorded census and population movement without large loss to follow-up
Selective reporting (reporting bias)	Low risk	Random sampling of clusters of 200 people for the parasitological surveys
Other bias	Low risk	No other bias detected

Paik 1974a SLB

Methods	<p>Dates of study: 1972</p> <p>Location of study: Solomon Islands (known as British Solomon Islands at the time of the study's publication)</p> <p>Malaria endemicity (prevalence): 27.8% all ages (May 1972 survey) [Moderate]</p> <p>Transmission season: Rainy season December to April</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. vivax</i></p> <p>Vector species: <i>A. farauti</i></p> <p>Study design: Uncontrolled before-and-after study</p> <p>Evaluation design: Cross-sectional surveys, passive surveillance and active surveillance</p>
Participants	<p>Age groups included: All ages</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): Not specified</p>
Interventions	Intervention group 1 (Nggela archipelago): MDA administered to all persons with chloroquine 600 mg and pyrimethamine 50 mg monthly for four months from July to October 1972. Coverage 90%. Co-intervention with IRS.
Outcomes	<p>Parasitaemia prevalence (includes both passive and active case detection for the period during and after the intervention)</p> <p>Parasitaemia incidence (population size not given)</p> <p>No adverse event surveillance conducted</p> <p>No adverse events reported</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group

Mass drug administration for malaria (Review)

Paik 1974a SLB (Continued)

Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement
Selective reporting (reporting bias)	High risk	Only 50% of children 2-9 years old included in the pre-MDA and post-MDA household surveys
Other bias	High risk	Baseline surveillance did not include active case detection

Paik 1974b SLB

Methods	<p>Dates of study: 1972-1973</p> <p>Location of study: Solomon Islands (known as British Solomon Islands at the time of the study's publication)</p> <p>Malaria endemicity (incidence): 15/1000 baseline monthly incidence</p> <p>Transmission season: Rainy season December to April</p> <p>Malaria species: <i>P. vivax</i>, <i>P. malariae</i></p> <p>Vector species: <i>A. farauti</i></p> <p>Study design: Uncontrolled before-and-after study</p> <p>Evaluation design: Passive surveillance</p>
Participants	<p>Age groups included: All ages</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): 1200</p>
Interventions	<p>Intervention group 1 (Wagina and Shortland): MDA administered to all persons with chloroquine 1500 mg and primaquine 75 mg over five days every three months for three rounds from October 1972 to March 1973. Coverage 90%. No co-interventions.</p>
Outcomes	<p>Parasitaemia incidence</p> <p>No adverse event surveillance conducted</p> <p>No adverse events reported</p>

Mass drug administration for malaria (Review)

Paik 1974b SLB (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Low risk	No other bias detected

Ricosse 1959 BFA

Methods	Dates of study: 1958-1959 Location of study: Burkina Faso Malaria endemicity (prevalence): Intervention group 1 (March-May 1958 baseline survey): 15.3% in children 0-9 years [Moderate]; Intervention group 2 (March to May 1958 baseline survey): 56.0% in children 0-9 years [High] Transmission season: June to October Malaria species: <i>P. falciparum</i> , <i>P. malariae</i> Vector species: <i>A. gambiae</i> , <i>A. funestus</i> Study design: Uncontrolled before-and-after study Evaluation design: Cross-sectional surveys
Participants	Age groups included: All ages <u>Sample size</u>

Mass drug administration for malaria (Review)

Ricosse 1959 BFA (Continued)

Intervention group 1 (mean): 5000

Intervention group 2 (mean): 3000

Interventions	<p>Intervention group 1 (Zone A): MDA administered to all persons with pyrimethamine 50 mg every two weeks for eight rounds in June to September 1958. Coverage 82-91%. Co-intervention with IRS using DDT.</p> <p>Intervention group 2 (Zone B): MDA administered to all persons with pyrimethamine 50 mg every two weeks for eight rounds in June to September 1958. Coverage 82-91%. No co-interventions.</p>
Outcomes	<p>Parasitaemia prevalence</p> <p>Gametocyaemia prevalence</p> <p>No adverse event surveillance conducted</p> <p>No adverse events reported</p>
Notes	Outcomes assessed in sub-sample of treated population (0-9 years). Data presented in Table 1 was used in the meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	High risk	In Zone B, pyrimethamine distribution stopped on September 20th and resumed in October, so the study was unable to follow the entire evolution of resistance that apparently began during the fourth month of distribution. Also, the method of selection of children 2-9 years is unclear. They took monthly blood samples in all children 0-23 months, but due to the large sample size selected only a proportion of children 2-9 years to examine.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Complicated by resistance in the fourth month of MDA

Roberts 1964 KEN

Methods	<p>Dates of study: 1953-1954</p> <p>Location of study: Kenya</p> <p>Malaria endemicity (prevalence): 28% in 1953 [Moderate] and 22% in 1954 [Moderate] in all ages in Tiriki</p> <p>Transmission season: May to July</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. malariae</i></p> <p>Vector species: <i>A. gambiae</i>, <i>A. funestus</i></p> <p>Study design: Non-randomized controlled study</p> <p>Evaluation design: Cross-sectional surveys</p>
Participants	<p>Age groups included: All ages</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): 101,000</p> <p>Intervention group 2 (mean): 99,000</p> <p>Comparison group 1 (mean): Not specified</p> <p>Comparison group 2 (mean): Not specified</p>
Interventions	<p>Intervention group 1 (Nandi District 1953): MDA administered to all persons with pyrimethamine 50 mg once in May 1953. Coverage 95%. No co-intervention.</p> <p>Intervention group 2 (Nandi District 1954): MDA administered to all persons with pyrimethamine 50 mg once in May 1954. Coverage 95%. No co-intervention.</p> <p>Comparison group 1 (Tiriki control area 1953): No interventions</p> <p>Comparison group 2 (Tiriki control area 1954): No interventions</p>
Outcomes	<p>Parasitaemia prevalence</p> <p>No adverse event surveillance conducted</p> <p>No adverse events reported</p>
Notes	<p>Intended to control epidemics.</p> <p>In the methods, it states: "one hundred thick blood films were taken in treated and untreated areas from persons in each of the age groups 0-10 years, 11-20 years, and 21 years and older". Therefore, we assumed that the number of total patients examined was 300 for both intervention and comparison groups to determine the number of cases identified in our calculations for parasitaemia prevalence.</p> <p>Outcomes were assessed in a sub-sample of the treated population.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomized controlled study

Roberts 1964 KEN (Continued)

Allocation concealment (selection bias)	High risk	Non-randomized controlled study
Baseline imbalance (selection bias)	High risk	Higher baseline parasitaemia in the control area
Contamination protection	Low risk	Not described but trial area was very large
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not blinded but unclear if this impacted outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned but unclear if this impacted outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All inhabitants living in the selected area received treatment
Selective reporting (reporting bias)	Unclear risk	Unclear who or how many were included in the malaria surveys
Other bias	Low risk	No other bias detected

Schneider 1961 BFA

Methods	<p>Dates of study: 1960-1961</p> <p>Location of study: Burkina Faso</p> <p>Malaria endemicity (prevalence): Comparison group 1 (baseline survey): 59.4% in children 2-9 years [High]</p> <p>Transmission season: August to September</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. vivax</i></p> <p>Vector species: Not described</p> <p>Study design: Non-randomized controlled study (no pre-intervention measurements)</p> <p>Evaluation design: Cross-sectional surveys</p>
Participants	<p>Age groups included: All ages</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): 2500</p> <p>Intervention group 2 (mean): 3535</p> <p>Comparison group 1 (mean): Not specified</p>
Interventions	<p>Intervention group 1: MDA administered to all persons with a combination of 600 mg base chloroquine or amodiaquine and 15 mg base primaquine every 14 days in June to December 1960 for 15 rounds. No co-intervention. Coverage 90%.</p>

Schneider 1961 BFA (Continued)

Intervention group 2: MDA administered to all persons with 600 mg base amodiaquine and 15 mg base primaquine every 14 days in June to December 1960 for eight rounds. Coverage not specified. Co-intervention with IRS using DDT once a year in May 1960.

Comparison group 1: Control zone free of any intervention (house spraying or treatment). Coverage not specified.

Outcomes	Parasitaemia prevalence Gametocytaemia prevalence No adverse event surveillance conducted No adverse events reported
Notes	<p>Data on children 0-9 years were reported; however, data could only be abstracted for 2-9 years to draw appropriate comparisons. In addition, data for during MDA for the intervention groups were estimated using only October 1960 survey data; during MDA data for the comparison group was only provided for October 1960.</p> <p>Intervention sample size is based on the 2500 inhabitants of the three villages surveyed; half were randomized to receive amodiaquine and primaquine while the other half received chloroquine and primaquine.</p> <p>A third intervention group was treated with a combination of 600 mg base chloroquine or amodiaquine and 15 mg base primaquine every 14 days in June to December 1960; however, due to lack of detailed data presented, this group was not included in the meta-analysis.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomized controlled study
Allocation concealment (selection bias)	High risk	Non-randomized controlled study
Baseline imbalance (selection bias)	Low risk	Patient outcomes were measured prior to the intervention. According to investigators, no important differences were present across study groups.
Contamination protection	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Adults were treated during MDA, but were not included in the evaluation.
Selective reporting (reporting bias)	High risk	A monthly distribution schedule was also administered in the study; however due to the poor quality data, minimal results were described.
Other bias	Unclear risk	Insufficient information to permit judgement

Mass drug administration for malaria (Review)

Shekalaghe 2011 TZA

Methods	<p>Dates of study: 2008</p> <p>Location of study: Tanzania</p> <p>Malaria endemicity (prevalence): 0% in all ages [Low]</p> <p>Transmission season: March to May, October to November</p> <p>Malaria species: <i>P. falciparum</i></p> <p>Vector species: Not described</p> <p>Study design: Cluster-randomized trial</p> <p>Unit of randomization: Geographical clusters of households</p> <p>Adjusted analyses for clustering: Yes</p> <p>Adjustment method: Generalized estimating equations</p> <p>ICC: Not described</p> <p>Numbers of clusters: 16</p> <p>Number of people: 3457</p> <p>Average cluster size: 216</p> <p>Evaluation design: Cross-sectional surveys, passive surveillance and active surveillance in children</p>
Participants	<p>Age groups included: Ages > 1 year, but individuals who had received a full dose of ACT in the two weeks before the intervention were excluded.</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): 1110</p> <p>Comparison group 1 (mean): 2347</p>
Interventions	<p>Intervention group 1: MDA administered to all persons in eight clusters in four villages in Lower Moshi with sulphadoxine-pyrimethamine (25 mg + 1.25 mg/kg as a single dose on the first day) plus artesunate (4 mg/kg/day for three days) plus primaquine (0.75 mg/kg as a single dose on the third day). Pregnant women received sulphadoxine-pyrimethamine (25 mg + 1.25 mg/kg 25 mg + 1.25 mg/kg as a single dose on the first day) plus amodiaquine (10 mg/kg once daily for three days). Anaemic individuals received sulphadoxine-pyrimethamine (25 mg + 1.25 mg/kg 25 mg + 1.25 mg/kg as a single dose on the first day) plus artesunate (4 mg/kg/day for three days). Coverage 93%. Co-intervention with background bed net use (25.1% to 36.1%) and a single treatment campaign for trachoma with azithromycin was undertaken by a non-governmental organisation.</p> <p>Comparison group 1: Placebo administered to all persons in eight clusters once daily over three days. Coverage not described. Co-intervention with background bed net use (25.1% to 36.1%) and a single treatment campaign for trachoma with azithromycin was undertaken by a non-governmental organisation.</p>
Outcomes	<p>Parasitaemia prevalence</p> <p>Gametocyaemia prevalence</p> <p>Active adverse event surveillance with haemoglobin monitoring conducted in a subset of the population</p>

Shekalaghe 2011 TZA (Continued)

Adverse events reported: One individual was diagnosed with a severe skin reaction in the week following MDA. Upon review, it was determined that the event was drug related. A second individual presented with skin hyperpigmentation on the face, which was determined unrelated to drug treatment. Both individuals were treated with steroids and monitored until symptoms disappeared. In those given primaquine, moderate anaemia (Hb level of <8 g/dL) was observed in 40% (6/15 individuals) of the G6PD A-, 11.1% (3/27 individuals) of the G6PD A, and 4.5% (18/399 individuals) of the G6PD B individuals; one case of severe anaemia (Hb level of <5 g/dL) was observed.

Notes The prevalence outcomes were assessed in a sub-sample of the treated population.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized using computer generated randomization tables
Allocation concealment (selection bias)	Low risk	Not described, but low risk with the randomization of a small number of clusters presumably by the investigator
Baseline imbalance (selection bias)	Low risk	Baseline demographic and malaria characteristics were similar
Contamination protection	Low risk	Households that were located between clusters (ie within 1 km distance from the boundary of intervention and/or control clusters) were considered as buffer zones. Members of these households received the intervention in order to minimize contamination.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was used in the comparison arm
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The measurement of outcomes for intervention and comparison arms were identical.
Incomplete outcome data (attrition bias) All outcomes	Low risk	High coverage of intervention and population movement monitored
Selective reporting (reporting bias)	Low risk	For each cross-sectional survey, individuals were randomly selected from computer-generated random tables. All planned outcome measures were reported.
Other bias	Low risk	No other bias detected

Simeons 1938 IND

Methods

Dates of study: 1935

Location of study: India

Malaria endemicity (incidence): 156 cases/1000 baseline monthly incidence in all age groups

Transmission season: March to August

Simeons 1938 IND (Continued)

 Malaria species: *P. vivax*

 Vector species: *A. culicifacies*

Study design: Uncontrolled before-and-after study

Evaluation design: Passive surveillance

Participants	Age groups included: All ages <u>Sample size</u> Intervention group 1 (mean): 5650
Interventions	Intervention group 1 (Mill Area): MDA administered to all persons with atebtrin intramuscular 300 mg daily for 2 days and plasmochin simplex 60 mg daily for three days once in May to June 1935. Coverage 100%. Co-intervention with oiling for larval control after MDA.
Outcomes	Parasitaemia incidence Passive event surveillance conducted Adverse events reported: Haemoglobinuria occurred in 4 cases (2 severe and died; 2 mild); three of the cases were from the same household and all were taking treatment for syphilis. Fatal cases known to have syphilis and unlikely to be associated with atebtrin; although potentially associated with plasmochin. Abscesses reported in 49 small children and weak adults. "Giddiness" reported with atebtrin.
Notes	Baseline monthly incidence was estimated using survey data from May 1934 to April 1935 prior to MDA. Data used in the meta-analysis was extrapolated from graphs presented in the text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Every person in the Mill Area was treated; extensive propaganda was carried out to bring every fever case to the doctor.
Selective reporting (reporting bias)	Low risk	Passive surveillance data for the entire population was reported

Mass drug administration for malaria (Review)

Simeons 1938 IND (Continued)

Other bias	Low risk	No other bias detected
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Singh 1953 IND

Methods	Dates of study: 1952-1953 Location of study: India Malaria endemicity (prevalence): 22% in all ages [Moderate] Transmission season: September to November Malaria species: <i>P. falciparum</i> Vector species: Not described Study design: Non-randomized controlled study Evaluation design: Cross-sectional surveys and active surveillance
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Participants	Age groups included: All ages <u>Sample size</u> Intervention group 1 (mean): 125 Comparison group 1 (mean): 55 Comparison group 2 (mean): 121
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Interventions	Intervention group 1: MDA administered to all persons with amodiaquine 600 mg every two weeks for ten weeks starting in September 1952. Coverage not specified. No co-interventions. Comparison group 1 (comparison groups 1 and 2 combined): Neighboring control area. No co-interventions.
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Outcomes	Parasitaemia prevalence No adverse event surveillance conducted No adverse events reported
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Non-randomized controlled study
Allocation concealment (selection bias)	High risk	Non-randomized controlled study; selection of villages were made after initial survey. Communication facilities were taken into place to decide on the intervention.
Baseline imbalance (selection bias)	High risk	Baseline malaria characteristics were similar to comparison group 2 but not to comparison group 1.

Singh 1953 IND (Continued)

Contamination protection	High risk	Incidence of malaria was so high that every week large numbers of labourers were being repatriated to their own villages.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not blinded, but unclear if this impacted outcomes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not blinded, but unclear if this impacted outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	No description of intervention coverage
Selective reporting (reporting bias)	Low risk	Entire population surveyed
Other bias	Low risk	No other bias detected

Song 2010 KHM

Methods	<p>Dates of study: 2003-2006</p> <p>Location of study: Cambodia</p> <p>Malaria endemicity (prevalence): 55.8% in children < 16 years; 52.3% in all ages [High]</p> <p>Transmission season: Not described</p> <p>Malaria species: <i>P. falciparum</i>, <i>P. malariae</i>, <i>P. vivax</i></p> <p>Vector species: Not described</p> <p>Study design: Uncontrolled before-and-after study</p> <p>Evaluation design: Cross-sectional surveys</p>
Participants	<p>Age groups included: All ages</p> <p><u>Sample size</u></p> <p>Intervention group 1 (mean): 3653</p> <p>Intervention group 2 (mean): 2387</p>
Interventions	<p>Intervention group 1 (Kampong Speu, 17 villages, single round): MDA administered to all ages with artesunate 125 mg daily for two days, piperaquine 750 mg daily for two days and primaquine 9 mg every 10 days for six months starting in December 2003. Coverage not specified. No co-interventions.</p> <p>Intervention group 2 (Kampot, nine villages, two rounds on days 0 and 42): MDA administered to all ages with artesunate 125 mg daily for two days and piperaquine 750 mg daily for two days given on days 0 and 42 and primaquine 9 mg every 10 days for six months starting in December 2003. Coverage not specified. No co-interventions.</p>
Outcomes	<p>Parasitaemia prevalence</p> <p>Gametocyaemia prevalence</p>

Song 2010 KHM (Continued)

Passive event surveillance conducted

Adverse events reported: No adverse reactions reported to village malaria volunteers.

Notes

Kampot data was not included in meta-analysis as the denominator of children for the outcome data was not provided.

The outcomes were assessed in a sub-sample of the treated population.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	High risk	One village missing data from one year
Selective reporting (reporting bias)	High risk	Monitoring was different for the different villages. Some villages had missing data.
Other bias	Low risk	No other bias detected

van Dijk 1961 PNG

Methods

Dates of study: 1960

Location of study: Papua New Guinea

Malaria endemicity (prevalence): 38.6% in children 2-9 years (1959 survey); 18% in all ages (1959 and 1960 surveys) [Moderate]

Transmission season: Not described

 Malaria species: *P. falciparum*, *P. malariae*, *P. vivax*

 Vector species: *A. farauti*

Study design: Uncontrolled before-and-after study

Mass drug administration for malaria (Review)

van Dijk 1961 PNG (Continued)

Evaluation design: Cross-sectional surveys

Participants	Age groups included: All ages <u>Sample size</u> Intervention group 1 (mean): 1250
Interventions	Intervention group 1: MDA administered to all persons with chloroquine (450 mg) once every four weeks for 11 rounds. Coverage 97.2% (range 93.1% to 100%). Co-intervention with mass treatment of filariasis with diethylcarbamazine.
Outcomes	Parasitaemia prevalence Gametocytaemia prevalence No adverse event surveillance conducted No adverse events reported
Notes	Before MDA estimates include data from June 1959 and January 1960 surveys (Tables I and II). For intervention group 1, outcome estimates come from Table V.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No comparison group
Allocation concealment (selection bias)	High risk	No comparison group
Baseline imbalance (selection bias)	High risk	No comparison group
Contamination protection	High risk	No comparison group
Blinding of participants and personnel (performance bias) All outcomes	High risk	No comparison group
Blinding of outcome assessment (detection bias) All outcomes	High risk	No comparison group
Incomplete outcome data (attrition bias) All outcomes	High risk	Nine positives were not included in the 0-1 month post-MDA survey; they were not present during the last distribution.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes of interest have been reported
Other bias	Unclear risk	Visitors to the village were also treated with the group to which they were most closely related. Persons who stayed only a few days were not treated. However, it is unclear whether this introduced bias.

von Seidlein 2003 GMB

Methods	<p>Dates of study: 1999</p> <p>Location of study: Gambia</p> <p>Malaria endemicity: 42.9% in children ≤ 5 years [High]; describes 17-19% in all ages but this data was not from this study.</p> <p>Transmission season: June to December</p> <p>Malaria species: <i>P. falciparum</i></p> <p>Vector species: Not described</p> <p>Study design: Cluster-randomized trial</p> <p>Unit of randomization: Villages</p> <p>Adjusted analyses for clustering: Yes</p> <p>Adjustment method: Poisson regression model adjusting for population size</p> <p>ICC: Not described</p> <p>Number of clusters: 18 villages</p> <p>Number of people: 3655</p> <p>Average cluster size: 203</p> <p>Feature: Matched villages</p> <p>Evaluation design: Cross-sectional surveys, active surveillance and passive surveillance</p>
Participants	<p>Age groups included: Ages > 6 months old; non-pregnant</p> <p>A total of 16,442 people, of which 14,017 people (85%) were treated (placebo or MDA) including the buffer zone</p> <p><u>Sample size (of number evaluated)</u></p> <p>Intervention group 1 (mean): 1969</p> <p>Comparison group 1 (mean): 1686</p>
Interventions	<p>Intervention group 1: MDA administered to all non-pregnant persons aged > 6 months with sulfadoxine-pyrimethamine 1500 mg/75 mg and artesunate 200 mg once in June 1999. Coverage 89% in total population (90.8% in evaluated group). No co-interventions.</p> <p>Comparison group 1: Placebo administered to all non-pregnant persons aged > 6 months once in June 1999. Coverage 89% in total population (89.6% in evaluated group). No co-interventions.</p>
Outcomes	<p>Parasitaemia prevalence</p> <p>Parasitaemia incidence</p> <p>Gametocyaemia prevalence</p> <p>Anaemia prevalence (defined as hematocrit < 33%)</p> <p>Mortality</p> <p>Passive and active adverse event surveillance conducted</p> <p>Adverse events reported (passive surveillance system): 1 episode of pruritus</p>

von Seidlein 2003 GMB (Continued)

Adverse events reported (active surveillance system): 25 of 75 individuals remembered one or more complaints within 2 days of taking the drug including dizziness (13), fever (6), diarrhoea (5), vomiting (5) and itching (4).

Notes Incidence, gametocyte prevalence, anaemia prevalence and mortality reported for children only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	While the study is a cluster-randomized, double blind, placebo-controlled trial, the method of randomization is not described. Author correspondence revealed that randomization was computer generated.
Allocation concealment (selection bias)	Low risk	Drugs allocated to each of the 18 study villages were delivered to the study site in identical containers. One nurse was aware of the identity of the drugs, administered the drugs in the study villages and then left the study area.
Baseline imbalance (selection bias)	Low risk	Intervention and control villages did not differ appreciably in the demographic of malaria transmission characteristics.
Contamination protection	Low risk	All inhabitants of the non-randomized controlled villages in the study area were treated, to minimize possible dilution of the effect of the intervention.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Cluster-randomized, double blind, placebo-controlled trial; neither study personnel nor the study population were aware of which villages received placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cluster-randomized, double blind, placebo-controlled trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	All children in the surveillance villages were visited weekly; all 18 study villages that were randomized were analyzed.
Selective reporting (reporting bias)	Low risk	All primary and secondary endpoints reported
Other bias	Low risk	No other bias detected

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abraham 1944	Inadequate treatment dose
Afridi 1959	Inadequate treatment dose
Ahorlu 2009	Treatment not administered to entire population; intermittent preventive treatment for children (IPTc) study
Ahorlu 2011	Treatment not administered to entire population; intermittent preventive treatment for children (IPTc) study

Mass drug administration for malaria (Review)

Study	Reason for exclusion
Aikins 1993	Inadequate treatment dose; knowledge, attitudes, and prevention component of an individually randomized study
Alicata 1955	Inadequate treatment dose; individually randomized study
Aliev 2000	Inadequate treatment dose
Aliev 2001	Inadequate treatment dose
Allen 1990	Inadequate treatment dose
Alonso 1993a	Inadequate treatment dose; individually randomized study
Alonso 1993b	Inadequate treatment dose; individually randomized study
Alving 1952	Individually randomized study; study participants did not remain in endemic area
Amangel'diev 2001	Inadequate treatment dose; testing conducted prior to treatment; insufficient information on drug administration
Annual Report 1932	Inadequate treatment dose
Archambeault 1954	Study participants did not remain in endemic area
Archibald 1956	Individually randomized study
Babione 1966	Insufficient information on drug administration
Banerjea 1949	Inadequate treatment dose
Barber 1932	Inadequate treatment dose
Barger 2009	Individually randomized study
Baukapur 1984	Insufficient information on drug administration
Berberian 1948	Testing conducted prior to treatment
Berny 1936	Inadequate treatment dose
Bloch 1982	Insufficient information on drug administration
Bojang 2009	Insufficient information on outcomes reported
Bojang 2010	Individually randomized study
Bojang 2011	Insufficient information on outcomes reported
Boulanger 2009	Individually randomized study
Boulanger 2010	Individually randomized study
Brink 1958	Inadequate treatment dose
Butler 1943	Insufficient information on drug administration

Study	Reason for exclusion
Canet 1936	Inadequate treatment dose
Canet 1939	Insufficient information on outcomes reported
Canet 1949	Insufficient information on drug administration; insufficient information on outcomes reported (no outcome of interest reported)
Canet 1952	Inadequate treatment dose
Canet 1953	Inadequate treatment dose
Capponi 1953	Inadequate treatment dose
Celli 1914	Insufficient information on drug administration
Charles 1958	Individually randomized study; testing conducted prior to treatment
Charles 1960	Inadequate treatment dose
Charles 1962	Inadequate treatment dose
Chaudhuri 1950	Inadequate treatment dose
Chen 1999	Insufficient information on outcomes reported; treatment not administered to entire population
Cisse 2006	Individually randomized study
Cisse 2009	Treatment not administered to entire population; intermittent preventive treatment for children (IPTc) study
Ciuca 1937	Mixed curative and prophylactic dosing
Clark 1942	Testing conducted prior to treatment
Clarke 2008	Treatment not administered to entire population; intermittent preventive treatment for children (IPTc) study
Clyde 1958	Insufficient information on drug administration
Clyde 1961a	Insufficient information on outcomes reported
Clyde 1961b	Insufficient information on outcomes reported
Clyde 1962	Inadequate treatment dose
Coutinho 1962	Inadequate treatment dose
D'Anfreville 1930	Insufficient information on drug administration; insufficient information on outcomes reported (no outcome of interest reported)
Danquah 2009	Individually randomized study
Dapeng 1996	Insufficient information on drug administration; insufficient information on outcomes reported
de Mello 1938	Inadequate treatment dose

Study	Reason for exclusion
Decourt 1935	Inadequate treatment dose; individually randomized study
Decourt 1936	Inadequate treatment dose
Delmont 1981	Inadequate treatment dose; individually randomized study
Desowitz 1987	Insufficient information on drug administration
Diallo 1977	Inadequate treatment dose
Diallo 1983	Treatment not administered to entire population; intermittent preventive treatment in children (IPTc) study
Dicko 2008	Individually randomized study; testing conducted prior to treatment
Dicko 2011	Individually randomized study
Dixon 1950	Inadequate treatment dose
Doi 1989	Individually randomized study; testing conducted prior to treatment
Dola 1974	Inadequate treatment dose
Doucet 1947	Inadequate treatment dose
Downs 1946	Study participants did not remain in endemic area
Dupoux 1937	Insufficient information on outcomes reported
Dupoux 1939	Inadequate treatment dose
Edeson 1957	Inadequate treatment dose
Farinaud 1934	Insufficient information on drug administration
Farinaud 1950	Inadequate treatment dose
Gaud 1949	Inadequate treatment dose
Gilroy 1952	Inadequate treatment dose
Gomez Mendoza 1960	Insufficient information on outcomes reported
Gribben 1933	Inadequate treatment dose
Gruer 1962	Insufficient information on drug administration; insufficient information on outcomes of interest
Gunther 1951	Inadequate treatment dose
Gunther 1952	Mixed curative and prophylactic dosing
Gusmao 1970	Inadequate treatment dose; individually randomized study
Han 2006	Inadequate treatment dose

Study	Reason for exclusion
Harwin 1973	Individually randomized study
Henderson 1934	Mixed curative and prophylactic dosing
Ho 1965	Insufficient information on outcomes reported (no outcome of interest reported)
Houel 1954b	Treatment not administered to entire population (children only)
Huehne 1971	Post-only outcomes reported
Janssens 1950	Inadequate treatment dose
Joncour 1956	Inadequate treatment dose
Kaneko 2010	Insufficient information on drug administration; insufficient information on outcomes reported.
Karimov 2008	Inadequate treatment dose
Kingsbury 1931	Inadequate treatment dose
Klopfner 1949	Inadequate treatment dose
Komp 1935	Testing conducted prior to treatment
Konate 2011	Individually randomized study
Kweku 2008	Individually randomized study
Kweku 2009	Insufficient information on outcomes reported; comparison of delivery strategies; treatment not administered to entire population (both arms included intermittent preventive treatment in children (IPTc))
Lacroix 1952	Inadequate treatment dose
Lahon 1960	Inadequate treatment dose
Laing 1970	Testing conducted prior to treatment
Laing 1984	Inadequate treatment dose
Lakshmanacharyulu 1968	Insufficient information on drug administration
Levenson 1943	Mixed curative and prophylactic dosing
Liljander 2010	Individually randomized study
Lui 1986	Mixed curative and prophylactic dosing
Lysenko 1960	Mixed curative and prophylactic dosing
MacCormack 1983	Inadequate treatment dose
Mackerras 1954	Inadequate treatment dose
Maiga 2009	Individually randomized study

Study	Reason for exclusion
Malaria_Army 1934	Inadequate treatment dose; insufficient information on outcomes reported
Mason 1973	Insufficient information on drug administration
Mason 1977	Insufficient information on drug administration
Mastbaum 1957a	Inadequate treatment dose
Mastbaum 1957b	Inadequate treatment dose
McGregor 1966	Individually randomized study; testing conducted prior to treatment
Melik-Adamian 1938	Testing conducted prior to treatment
Mendez Galvan 1984	Insufficient information on drug administration; insufficient information on outcomes reported
Mercier 1953	Inadequate treatment dose
Merle 1955	Inadequate treatment dose; treatment not administered to entire population (eg intermittent preventive treatment for children (IPTc))
Mezincesco 1935	Inadequate treatment dose
Miller 1955	Inadequate treatment dose; individually randomized study; treatment not administered to entire population
Monteny 1960	Inadequate treatment dose
Mühlens 1913	Insufficient information on drug administration; insufficient information on outcomes of interest
Nakibuuka 2009	Individually randomized study; testing conducted prior to treatment
Nankabirwa 2010	Individually randomized study
Nave 1973	Insufficient information on outcomes reported
Norman 1952	Inadequate treatment dose; insufficient information on outcomes of interest
Ntab 2007	Individually randomized study; insufficient information on outcomes reported
Omer 1978	Inadequate treatment dose
Onori 1972	Inadequate treatment dose
Ossi 1967	Insufficient information on outcomes reported
Ouedraogo 2010	Individually randomized study
Parrot 1937	Inadequate treatment dose
Parrot 1943	Inadequate treatment dose
Parrot 1944	Inadequate treatment dose
Parrot 1946	Inadequate treatment dose

Study	Reason for exclusion
Peters 1962	Inadequate treatment dose
Phillips 1954	Inadequate treatment dose
Pikul 1934	Insufficient information on outcomes reported
Pribadi 1986	Inadequate treatment dose
Prokopenko 1945	Inadequate treatment dose
Rachou 1965	Inadequate treatment dose
Rafi 1951	Inadequate treatment dose
Ray 1948	Inadequate treatment dose
Robin 1946	Testing conducted prior to treatment
Rodríguez 1994	Testing conducted prior to treatment
Rohner 2010	Individually randomized study
Saarinen 1987	Mixed curative and prophylactic dosing
Salako 1990	Individually randomized study; testing conducted prior to treatment
Salihu 2000	Inadequate treatment dose
Santos 1993	Inadequate treatment dose
Schliessmann 1973	Insufficient information on outcomes reported
Schneider 1948a	Inadequate treatment dose
Schneider 1948b	Inadequate treatment dose
Schneider 1958	Inadequate treatment dose
Schneider 1962	Individually randomized study; treatment not administered to entire population (eg intermittent preventive treatment for children (IPTc))
Seckinger 1935	Inadequate treatment dose
Sehgal 1968	Insufficient information on drug administration
Sergent 1913	Inadequate treatment dose; insufficient information on outcomes reported
Sesay 2011	Individually randomized study
Shanks 1992	Inadequate treatment dose; individually randomized study; testing conducted prior to treatment
Shanks 1993	Individually randomized study; study participants did not remain in endemic area
Shanks 1995a	Inadequate treatment dose; study participants did not remain in endemic area

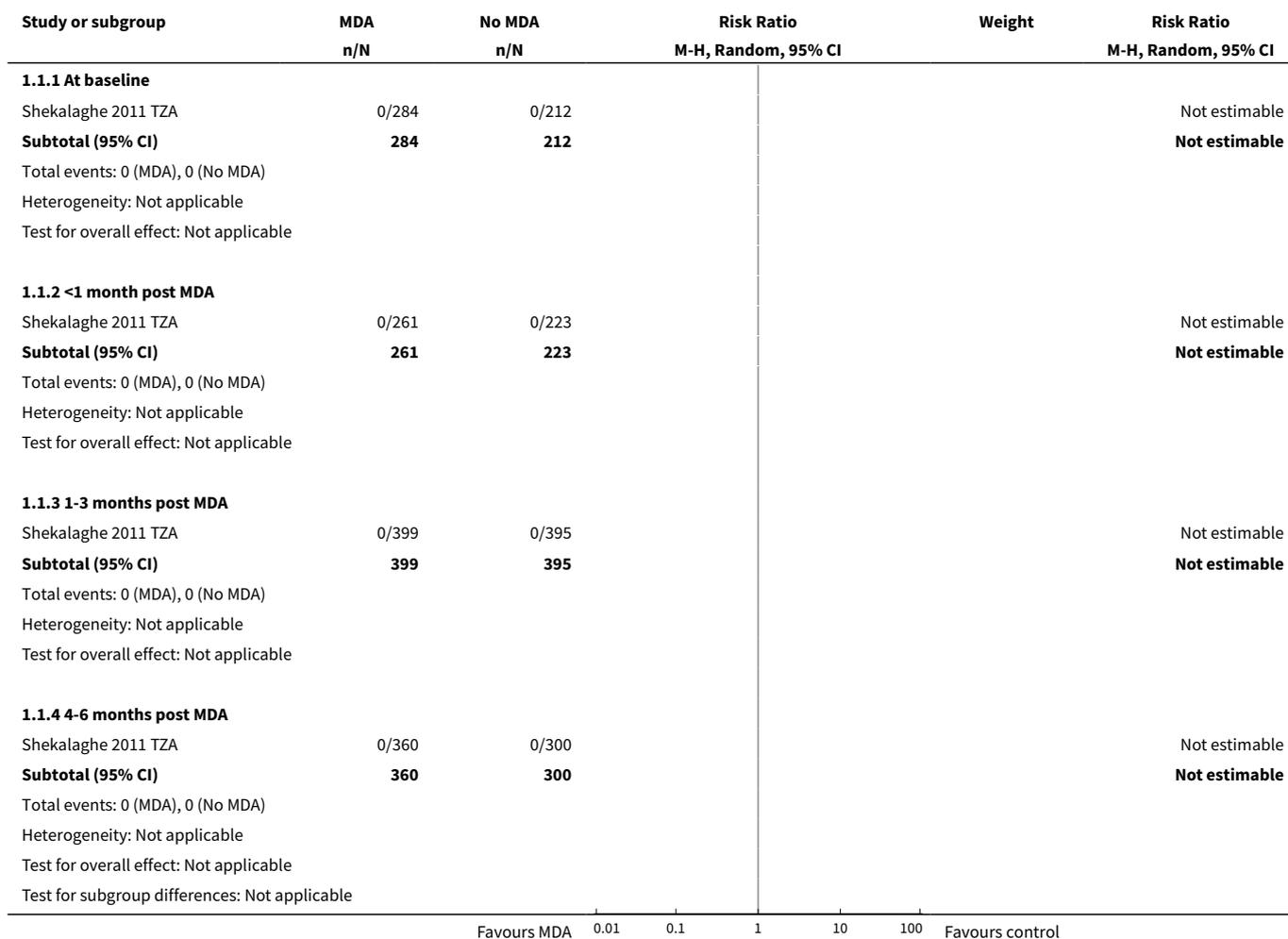
Study	Reason for exclusion
Shanks 1995b	Study participants did not remain in endemic area
Sheinker 1945	Testing conducted prior to treatment
Singh 1968	Insufficient information on outcomes reported
Snowden 2006	Insufficient information on drug administration; insufficient information on outcomes reported
Sokhna 2008	Individually randomized study
Sorel 1913	Insufficient information on drug administration
Srivastava 1950	Inadequate treatment dose
Strangeways-Dixon 1950	Inadequate treatment dose
Strickland 1986	Testing conducted prior to treatment
Swellengrebel 1931	Inadequate treatment dose
Tagbor 2011	Treatment not administered to entire population; intermittent preventive treatment for children (IPTc) study
Tine 2011	Treatment not administered to entire population; intermittent preventive treatment for children (IPTc) study
Turner 1977	Insufficient information on outcomes reported
Usenbaev 2006	Insufficient information on drug administration
Usenbaev 2008	Insufficient information on drug administration
Van Dijk 1958	Inadequate treatment dose
Van Goor 1950	Inadequate treatment dose
Verhoef 2002	Individually randomized study
Villegas 2010	Testing conducted prior to treatment
Wallace 1936	Mixed curative and prophylactic dosing
Wallace 1954	Insufficient information on drug administration
Watkins 1987	Individually randomized; mixed curative and prophylactic dosing
White 1934	Inadequate treatment dose
White 1937	Mixed curative and prophylactic dosing
Winter 1934	Insufficient information on outcomes reported
Wone 1967	Inadequate treatment dose
Yip 1998	Insufficient information on outcomes reported

DATA AND ANALYSES

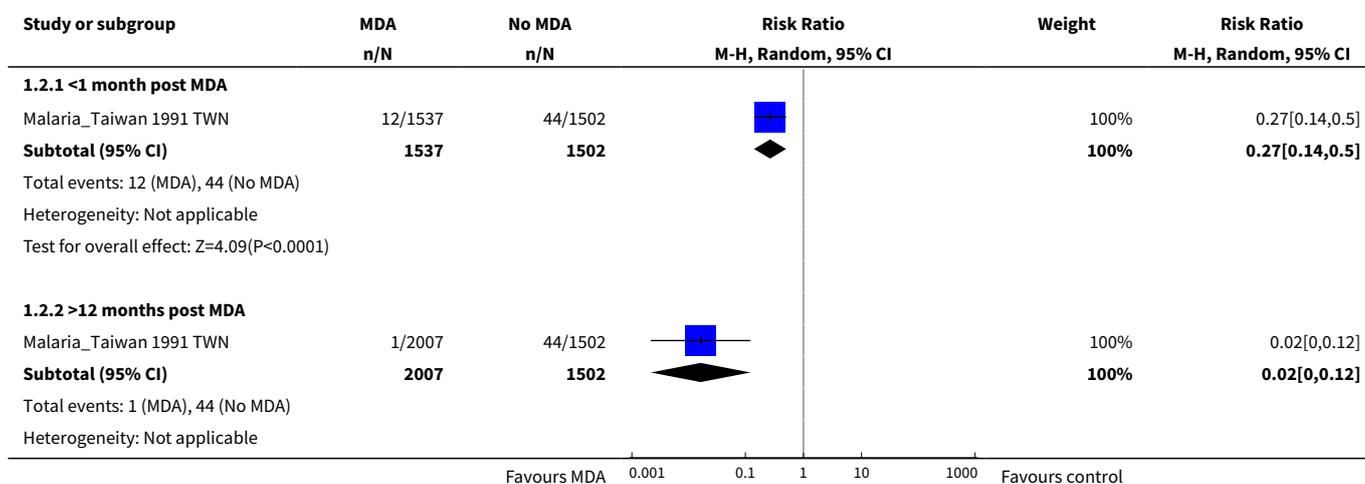
Comparison 1. MDA versus no MDA in areas of low endemicity (Stratified by study design)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia Prevalence: Cluster-randomized trials	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 At baseline	1	496	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 <1 month post MDA	1	484	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 1-3 months post MDA	1	794	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 4-6 months post MDA	1	660	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Parasitaemia Prevalence: Uncontrolled before-and-after studies	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 <1 month post MDA	1	3039	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.14, 0.50]
2.2 >12 months post MDA	1	3509	Risk Ratio (M-H, Random, 95% CI)	0.02 [0.00, 0.12]
3 Gametocyaemia Prevalence: Cluster randomized trials	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 At baseline	1	496	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 < 1 month post MDA	1	484	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 1-3 months post MDA	1	794	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.4 4-6 months post MDA	1	660	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 MDA versus no MDA in areas of low endemicity (Stratified by study design), Outcome 1 Parasitaemia Prevalence: Cluster-randomized trials.



Analysis 1.2. Comparison 1 MDA versus no MDA in areas of low endemicity (Stratified by study design), Outcome 2 Parasitaemia Prevalence: Uncontrolled before-and-after studies.



Study or subgroup	MDA n/N	No MDA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=4.03(P<0.0001)					
Test for subgroup differences: Chi ² =6.72, df=1 (P=0.01), I ² =85.13%					
Favours MDA 0.001 0.1 1 10 1000 Favours control					

Analysis 1.3. Comparison 1 MDA versus no MDA in areas of low endemicity (Stratified by study design), Outcome 3 Gametocytaemia Prevalence: Cluster randomized trials.

Study or subgroup	MDA n/N	No MDA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 At baseline					
Shekalaghe 2011 TZA	0/284	0/212			Not estimable
Subtotal (95% CI)	284	212			Not estimable
Total events: 0 (MDA), 0 (No MDA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.3.2 < 1 month post MDA					
Shekalaghe 2011 TZA	0/261	0/223			Not estimable
Subtotal (95% CI)	261	223			Not estimable
Total events: 0 (MDA), 0 (No MDA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.3.3 1-3 months post MDA					
Shekalaghe 2011 TZA	0/399	0/395			Not estimable
Subtotal (95% CI)	399	395			Not estimable
Total events: 0 (MDA), 0 (No MDA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.3.4 4-6 months post MDA					
Shekalaghe 2011 TZA	0/360	0/300			Not estimable
Subtotal (95% CI)	360	300			Not estimable
Total events: 0 (MDA), 0 (No MDA)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					
Favours MDA 0.01 0.1 1 10 100 Favours control					

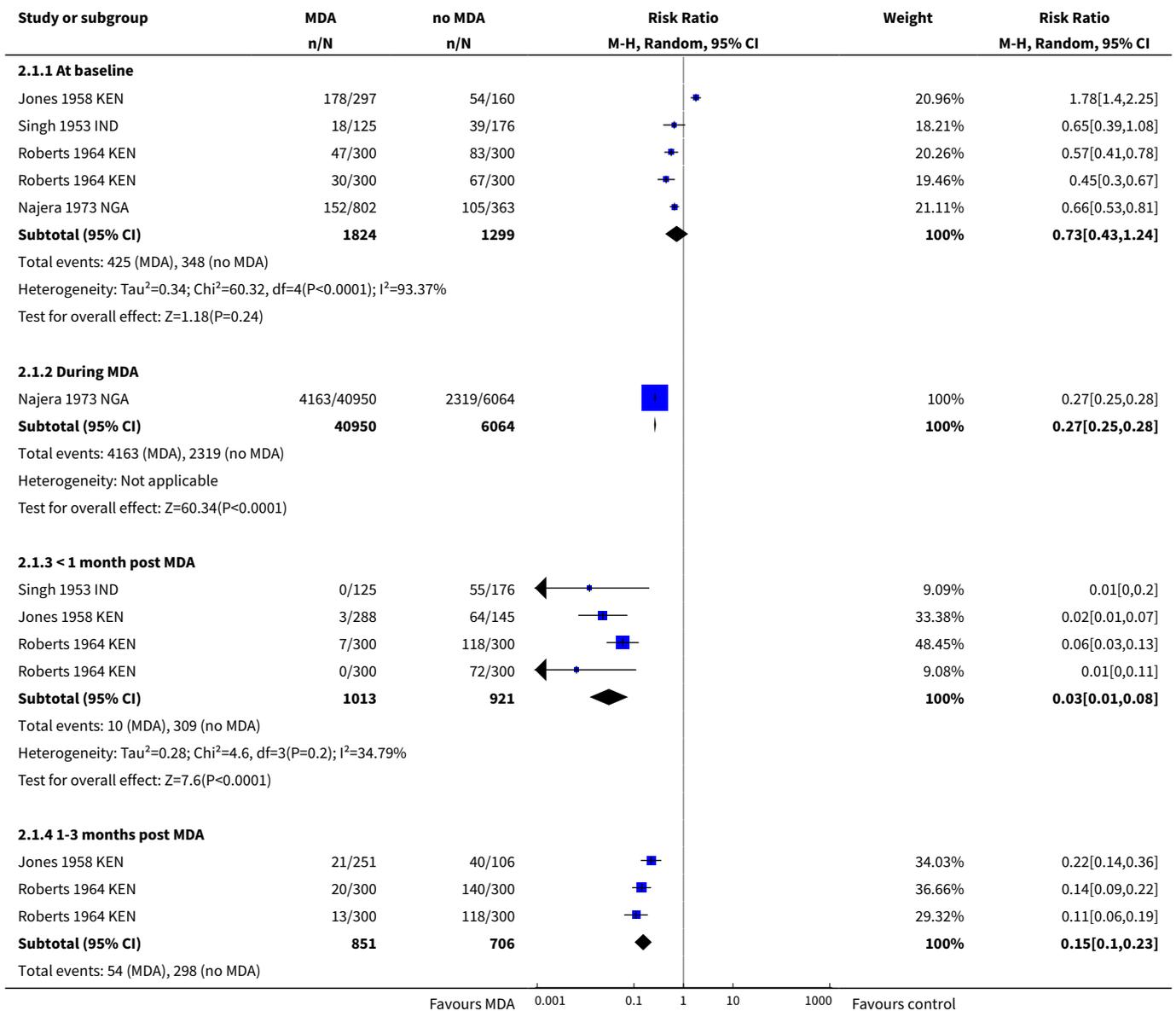
Comparison 2. MDA versus no MDA in areas of moderate endemicity (Stratified by study design)

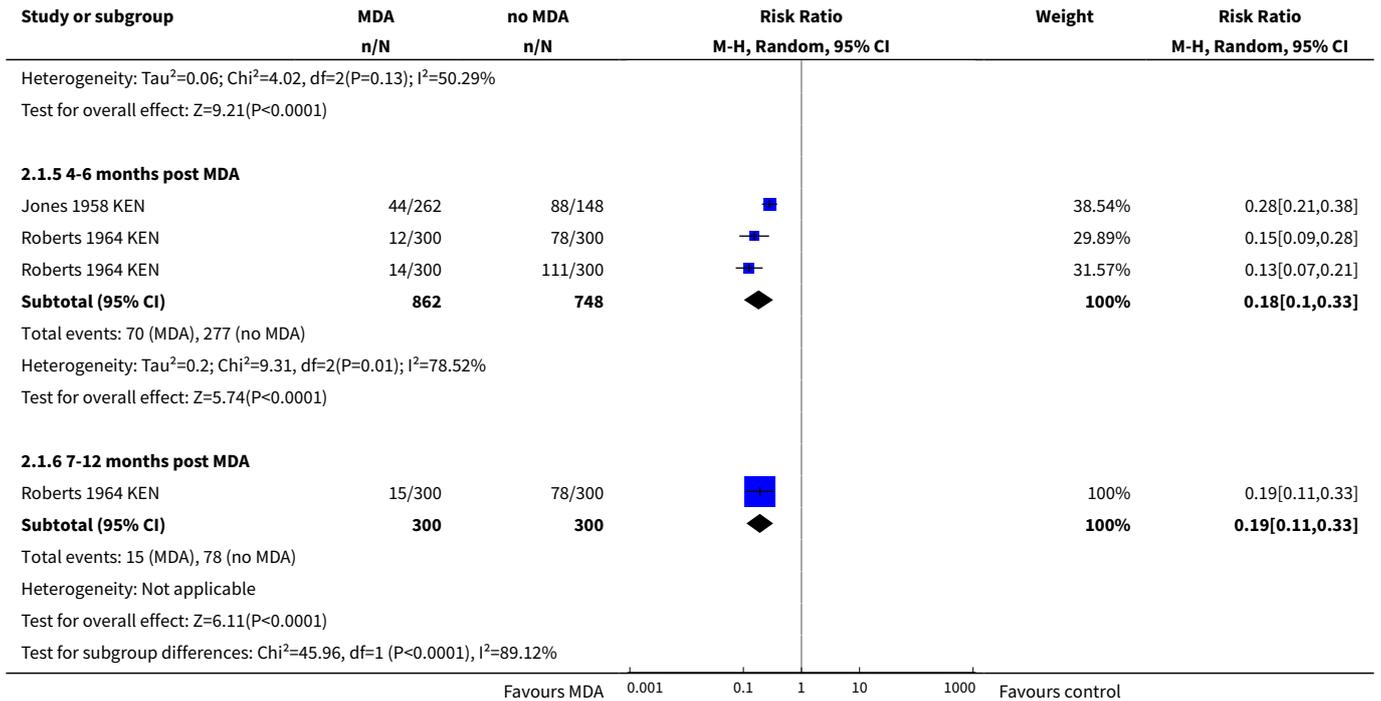
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia Prevalence: Non-randomized controlled studies	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 At baseline	4	3123	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.43, 1.24]
1.2 During MDA	1	47014	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.25, 0.28]
1.3 < 1 month post MDA	3	1934	Risk Ratio (M-H, Random, 95% CI)	0.03 [0.01, 0.08]
1.4 1-3 months post MDA	2	1557	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.10, 0.23]
1.5 4-6 months post MDA	2	1610	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.10, 0.33]
1.6 7-12 months post MDA	1	600	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.11, 0.33]
2 Parasitaemia Prevalence: Uncontrolled before-and-after studies	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 During MDA	2	7965	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.02, 1.47]
2.2 <1 month post MDA	3	3096	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.17, 0.48]
2.3 1-3 months post MDA	4	7925	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.08, 0.31]
2.4 4-6 months post MDA	2	3797	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.41, 7.41]
3 Gametocytaemia Prevalence: Non-randomized controlled studies	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 At baseline	2	1622	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.76, 2.57]
3.2 During MDA	1	47014	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.42, 0.54]
3.3 <1 month post MDA	1	433	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.10, 0.82]
3.4 1-3 months post MDA	1	357	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.03, 0.86]
3.5 4-6 months post MDA	1	410	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.24, 1.11]
4 Gametocytaemia Prevalence: Uncontrolled before-and-after studies	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

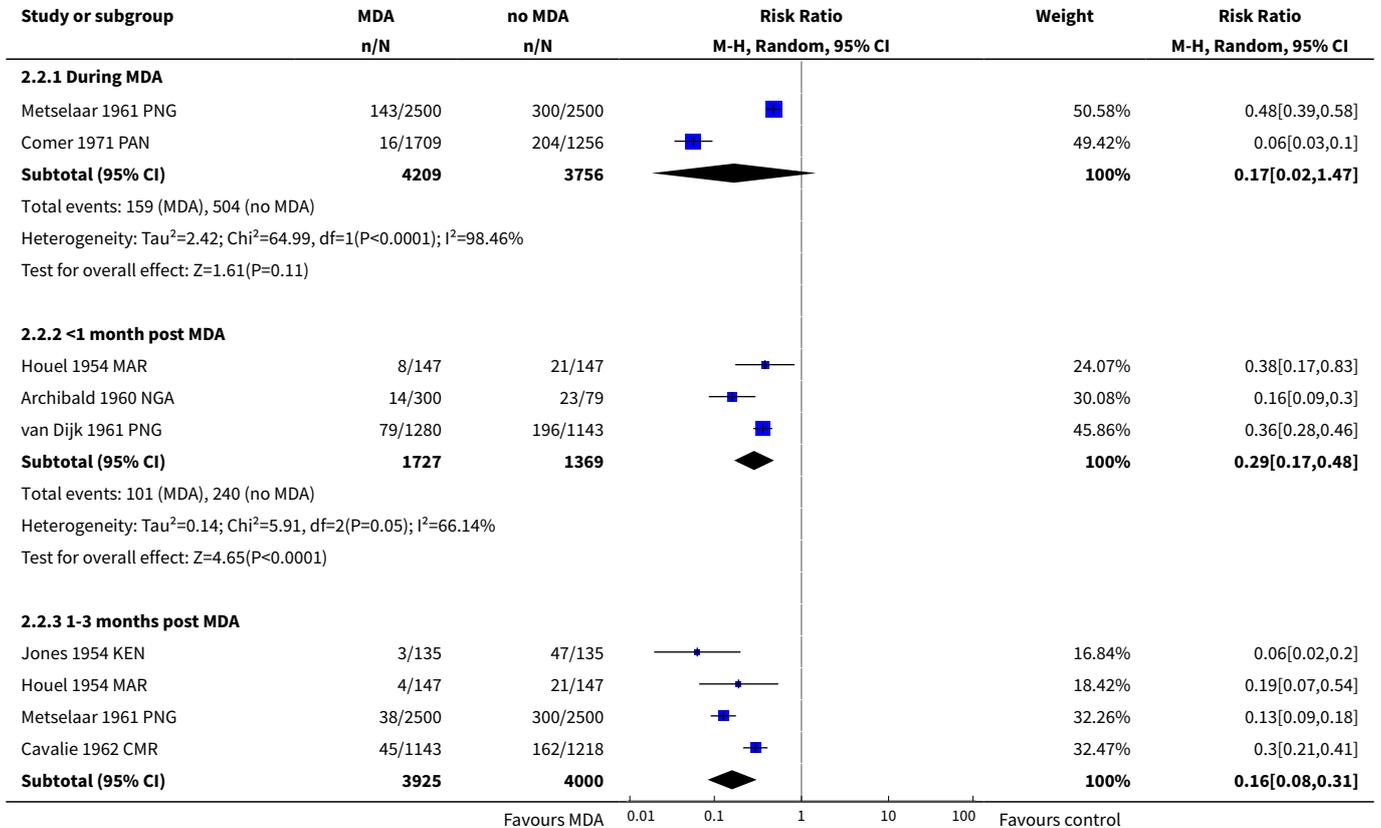
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 <1 month post MDA	3	3096	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.25, 0.87]
4.2 1-3 months post MDA	1	294	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.12, 1.12]
4.3 4-6 months post MDA	1	204	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.12, 1.01]

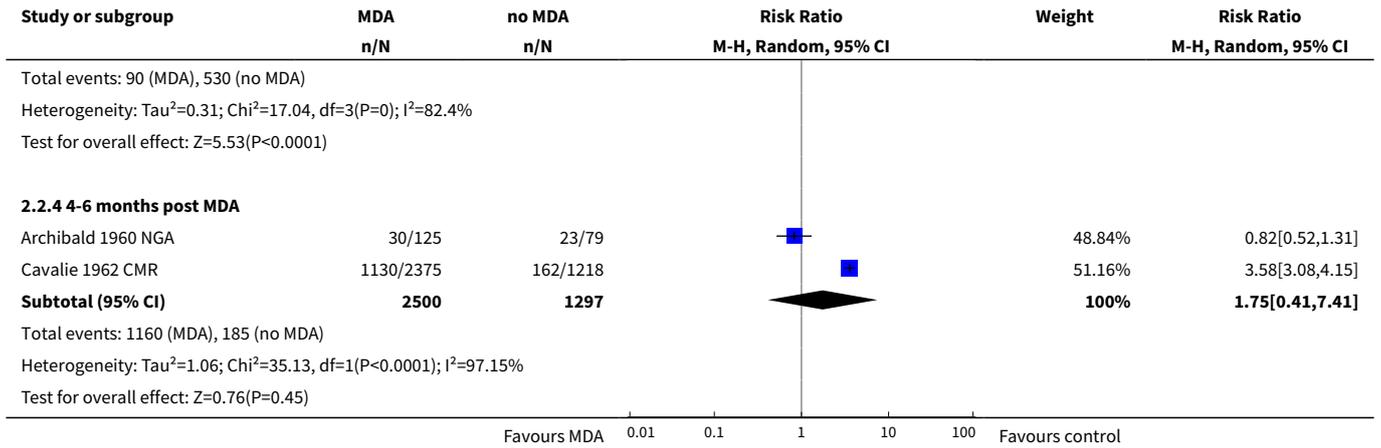
Analysis 2.1. Comparison 2 MDA versus no MDA in areas of moderate endemicity (Stratified by study design), Outcome 1 Parasitaemia Prevalence: Non-randomized controlled studies.



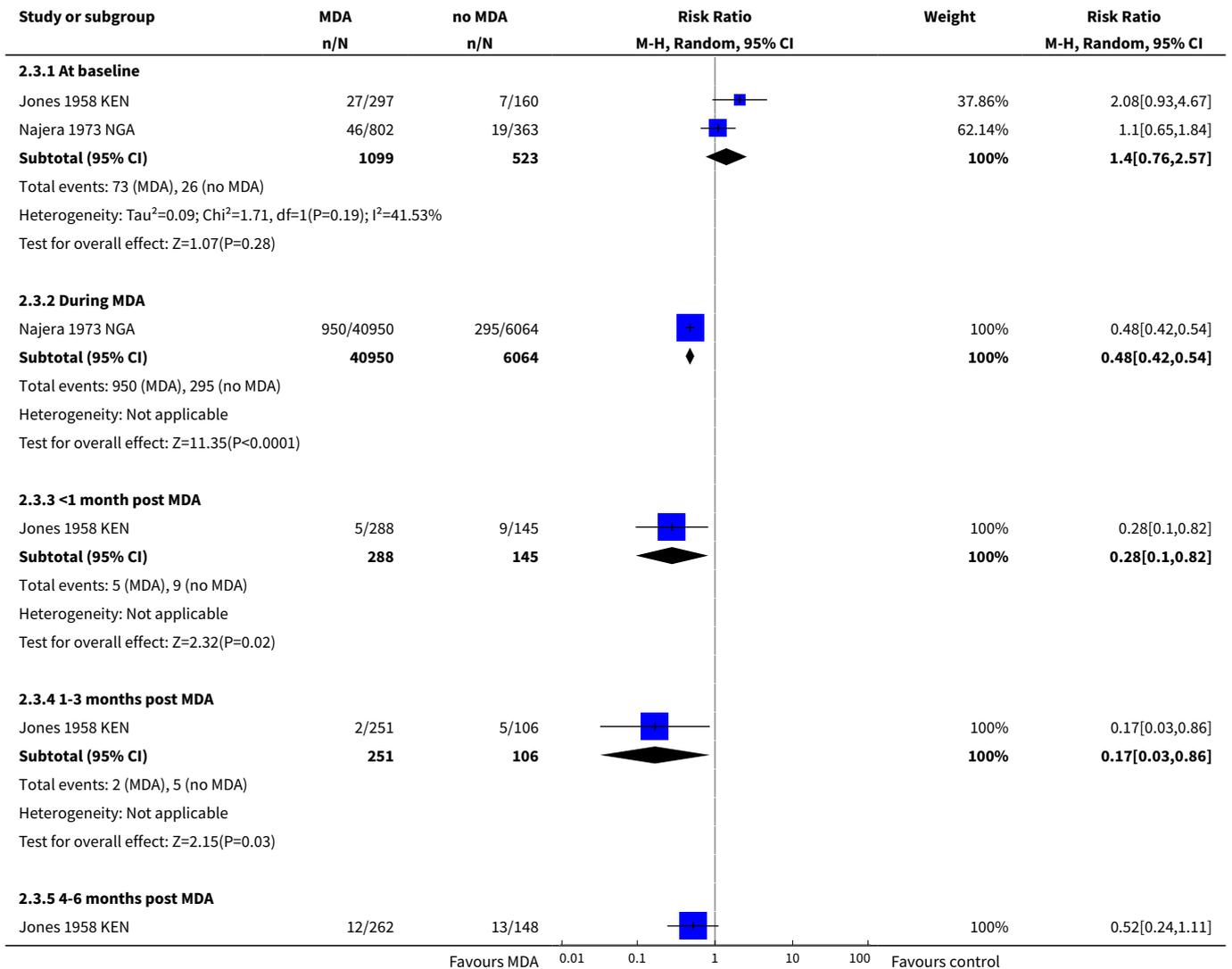


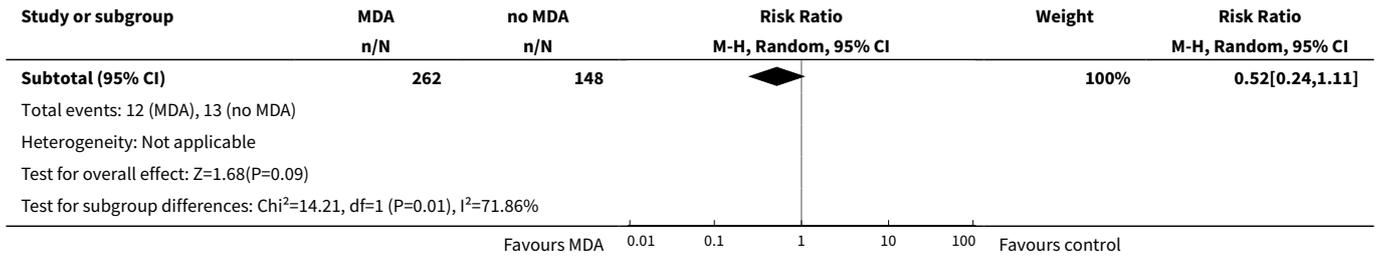
Analysis 2.2. Comparison 2 MDA versus no MDA in areas of moderate endemicity (Stratified by study design), Outcome 2 Parasitaemia Prevalence: Uncontrolled before-and-after studies.



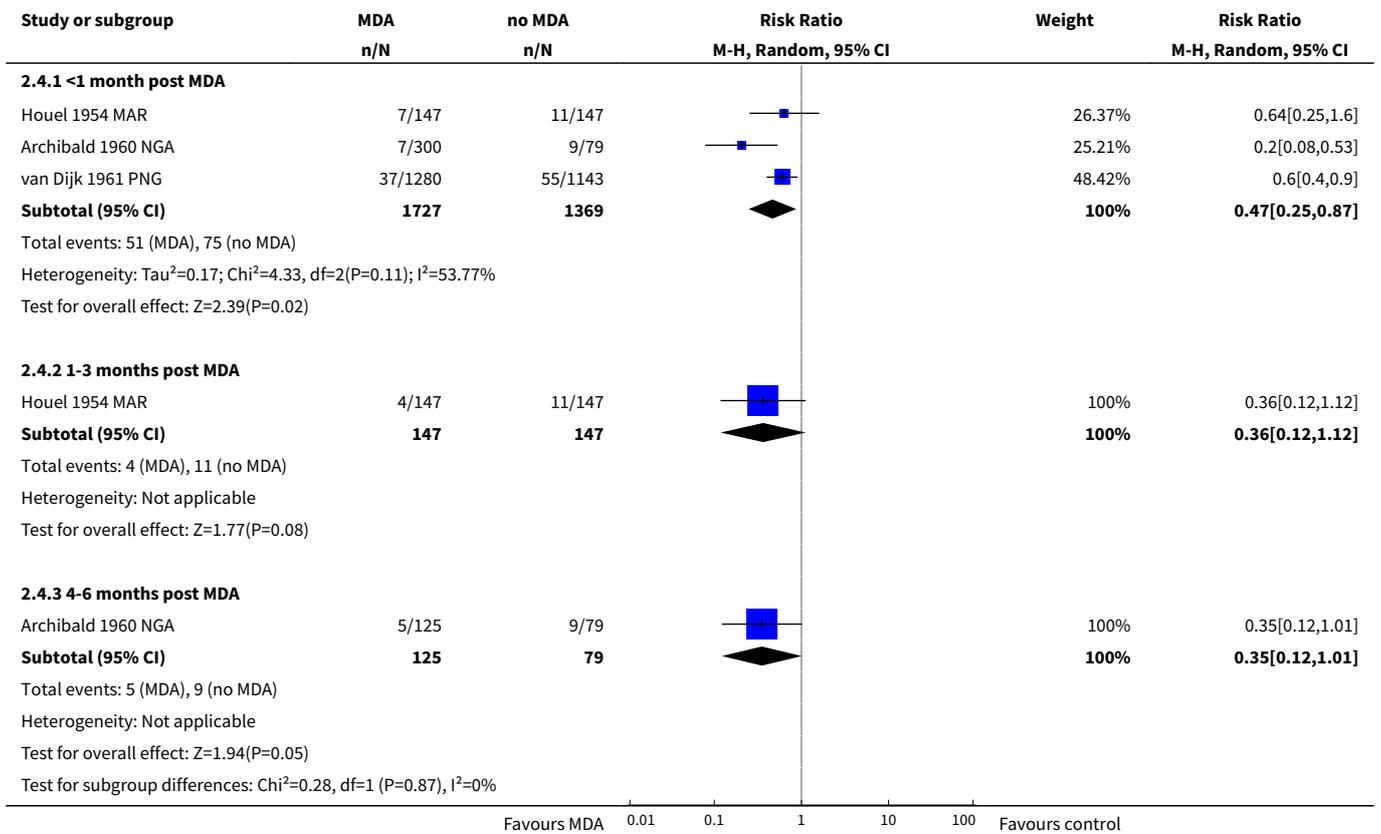


Analysis 2.3. Comparison 2 MDA versus no MDA in areas of moderate endemicity (Stratified by study design), Outcome 3 Gametocytaemia Prevalence: Non-randomized controlled studies.





Analysis 2.4. Comparison 2 MDA versus no MDA in areas of moderate endemicity (Stratified by study design), Outcome 4 Gametocytaemia Prevalence: Uncontrolled before-and-after studies.



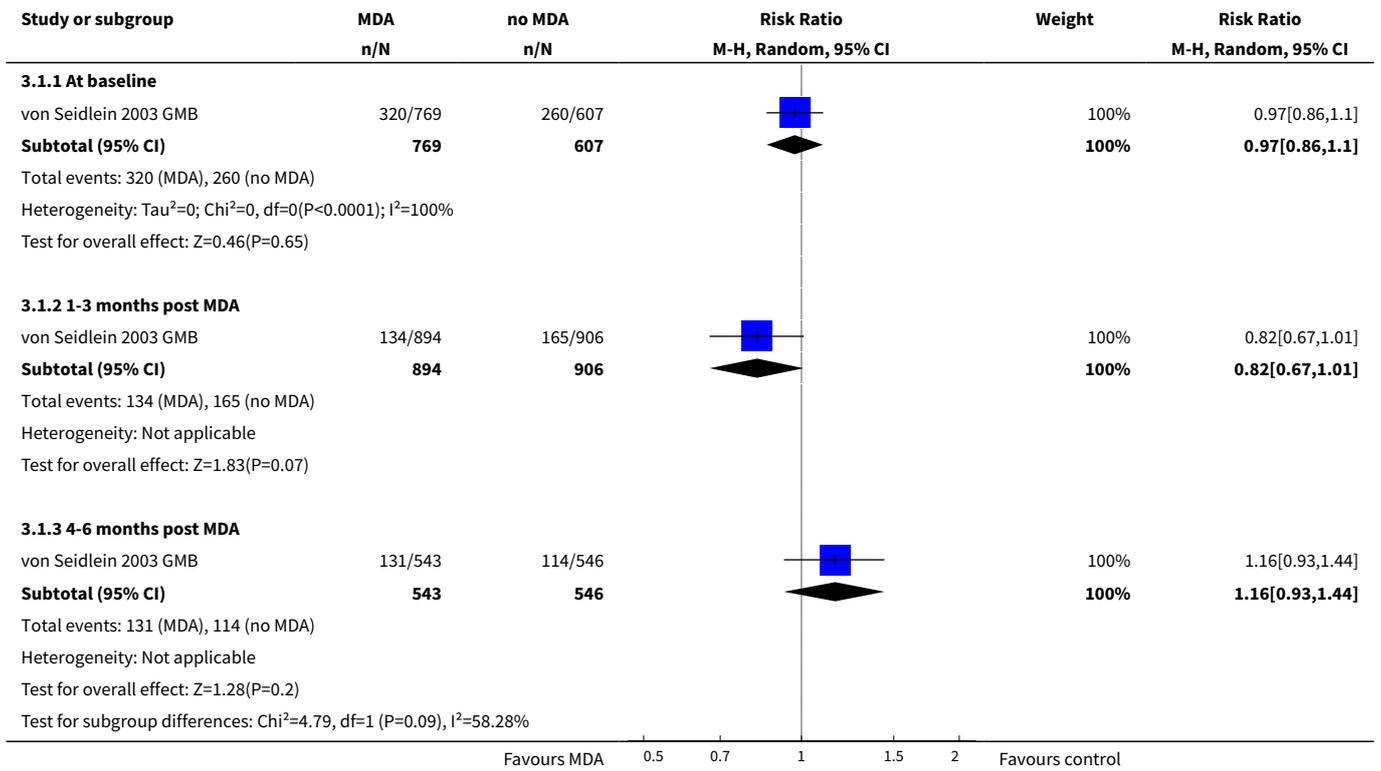
Comparison 3. MDA versus no MDA in areas of high endemicity (Stratified by study design)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia Prevalence: Cluster-randomized trials	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 At baseline	1	1376	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.86, 1.10]

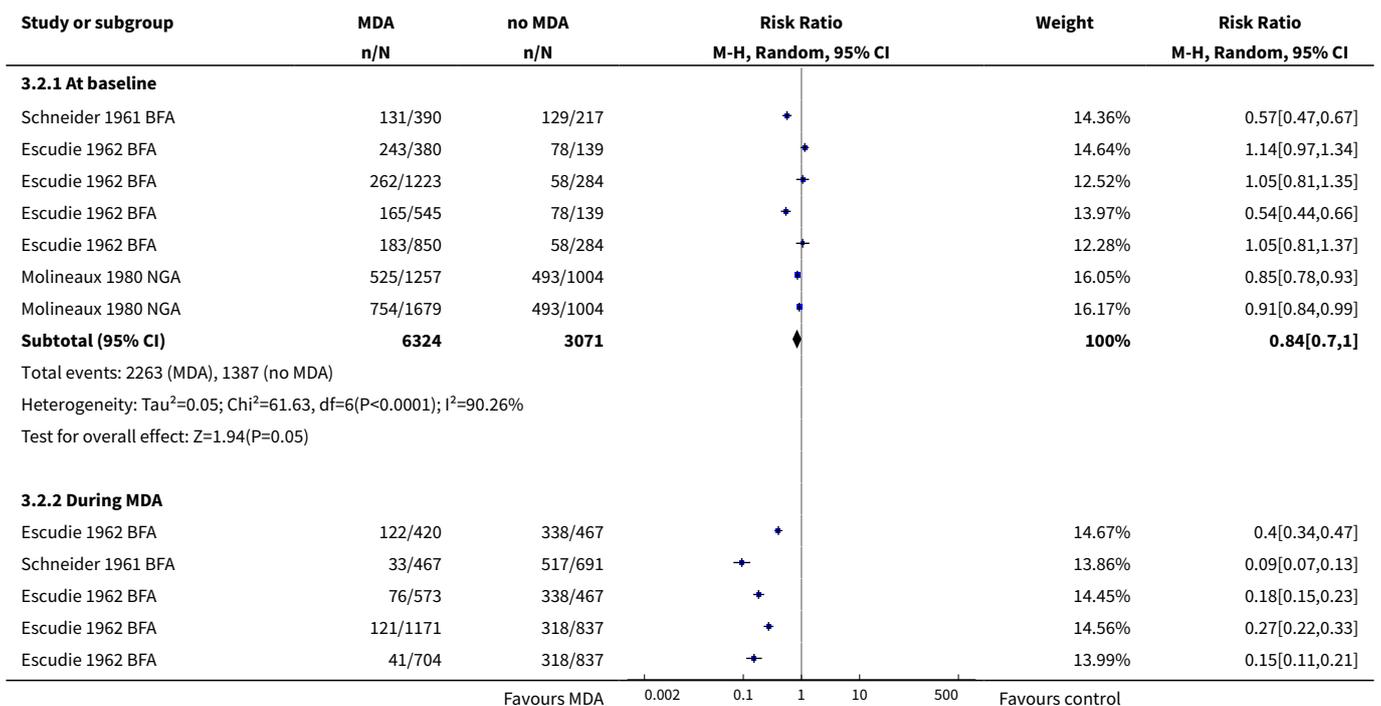
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 1-3 months post MDA	1	1800	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.67, 1.01]
1.3 4-6 months post MDA	1	1089	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.93, 1.44]
2 Parasitaemia Prevalence: Non-randomized controlled studies	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 At baseline	3	9395	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.70, 1.00]
2.2 During MDA	3	12561	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.11, 0.27]
2.3 1-3 months post MDA	2	7197	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.33, 0.81]
3 Parasitaemia Prevalence: Uncontrolled before-and-after studies	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 During MDA	2	2011	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.03, 0.34]
3.2 <1 month post MDA	4	3863	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.28, 0.49]
3.3 1-3 months post MDA	4	5132	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.15, 0.84]
3.4 4-6 months post MDA	3	2979	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.24, 0.72]
3.5 7-12 months post MDA	1	75	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.43, 1.20]
3.6 >12 months post MDA	1	2375	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.07, 0.12]
4 Parasitaemia Incidence: Cluster-randomized trials	1		Rate Ratio (Random, 95% CI)	0.84 [0.53, 1.32]
4.1 < 1 month post MDA	1		Rate Ratio (Random, 95% CI)	0.41 [0.23, 0.74]
4.2 1-3 months post MDA	1		Rate Ratio (Random, 95% CI)	1.03 [0.75, 1.41]
4.3 4-6 months post MDA	1		Rate Ratio (Random, 95% CI)	1.11 [0.84, 1.45]
5 Gametocyaemia Prevalence: Cluster-randomized trials	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 At baseline	1	1376	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.33, 1.29]

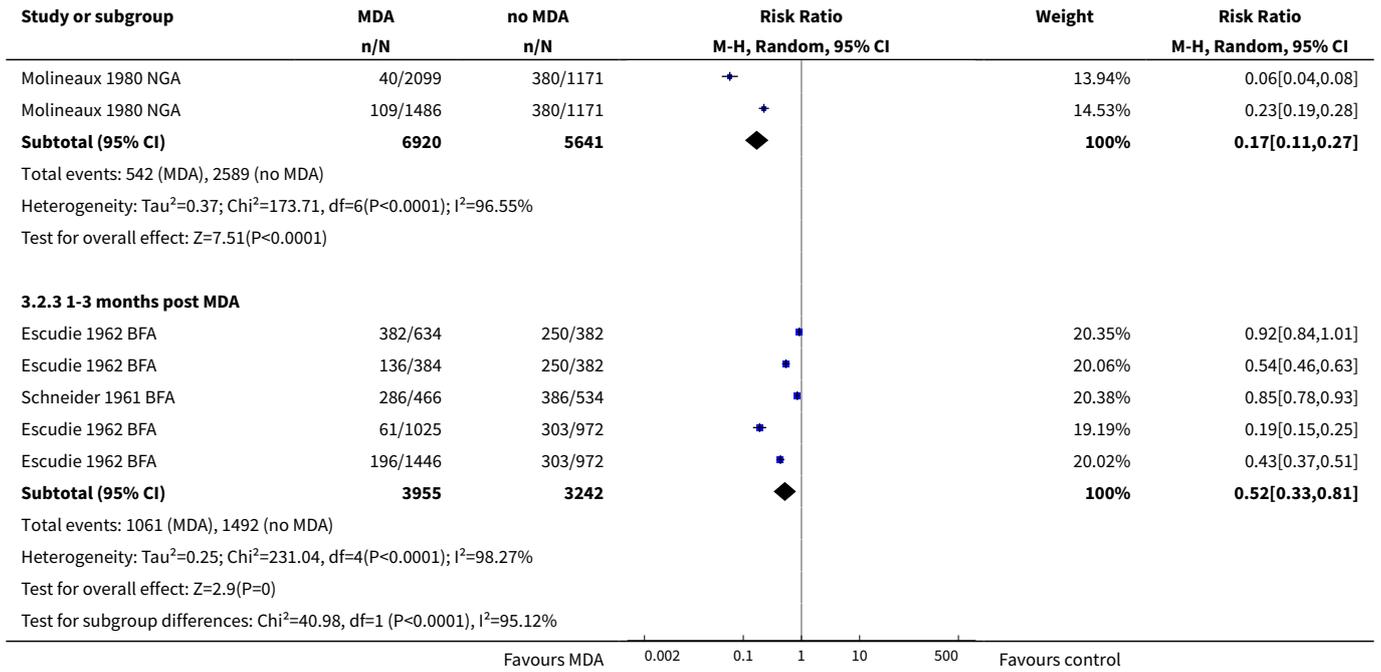
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 4-6 months post MDA	1	1414	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.62, 1.85]
6 Gametocytaemia Prevalence: Non-randomized controlled studies	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 At baseline	3	9395	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.55, 0.95]
6.2 During MDA	3	12561	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.10, 0.28]
6.3 1-3 months post MDA	2	7197	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.28, 1.07]
7 Gametocytaemia Prevalence: Uncontrolled before-and-after studies	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 During MDA	2	2011	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.09, 1.40]
7.2 <1 month post MDA	3	2582	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.13, 1.08]
7.3 1-3 months post MDA	2	1199	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.64, 2.01]
7.4 4-6 months post MDA	2	2789	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.10, 1.28]
7.5 7-12 months post MDA	1	75	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.41, 1.79]
7.6 >12 months post MDA	1	2269	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.05, 0.15]
8 Anaemia Prevalence: Cluster-randomized trials	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 4-6 months post MDA	1	1414	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.75, 0.93]
9 Mortality: Cluster-randomized trials	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 4-6 months post MDA	1	3655	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.34, 5.96]

Analysis 3.1. Comparison 3 MDA versus no MDA in areas of high endemicity (Stratified by study design), Outcome 1 Parasitaemia Prevalence: Cluster-randomized trials.

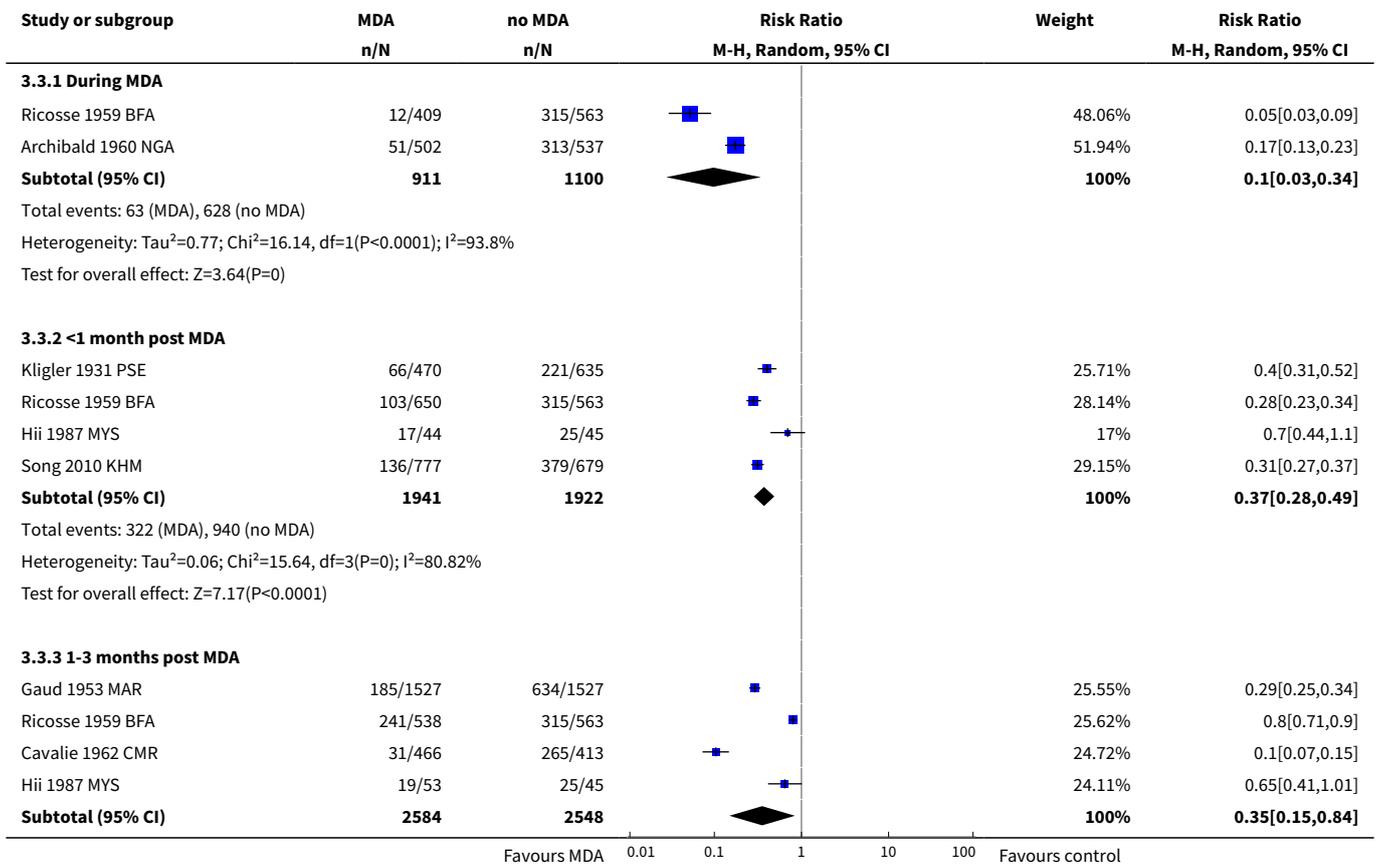


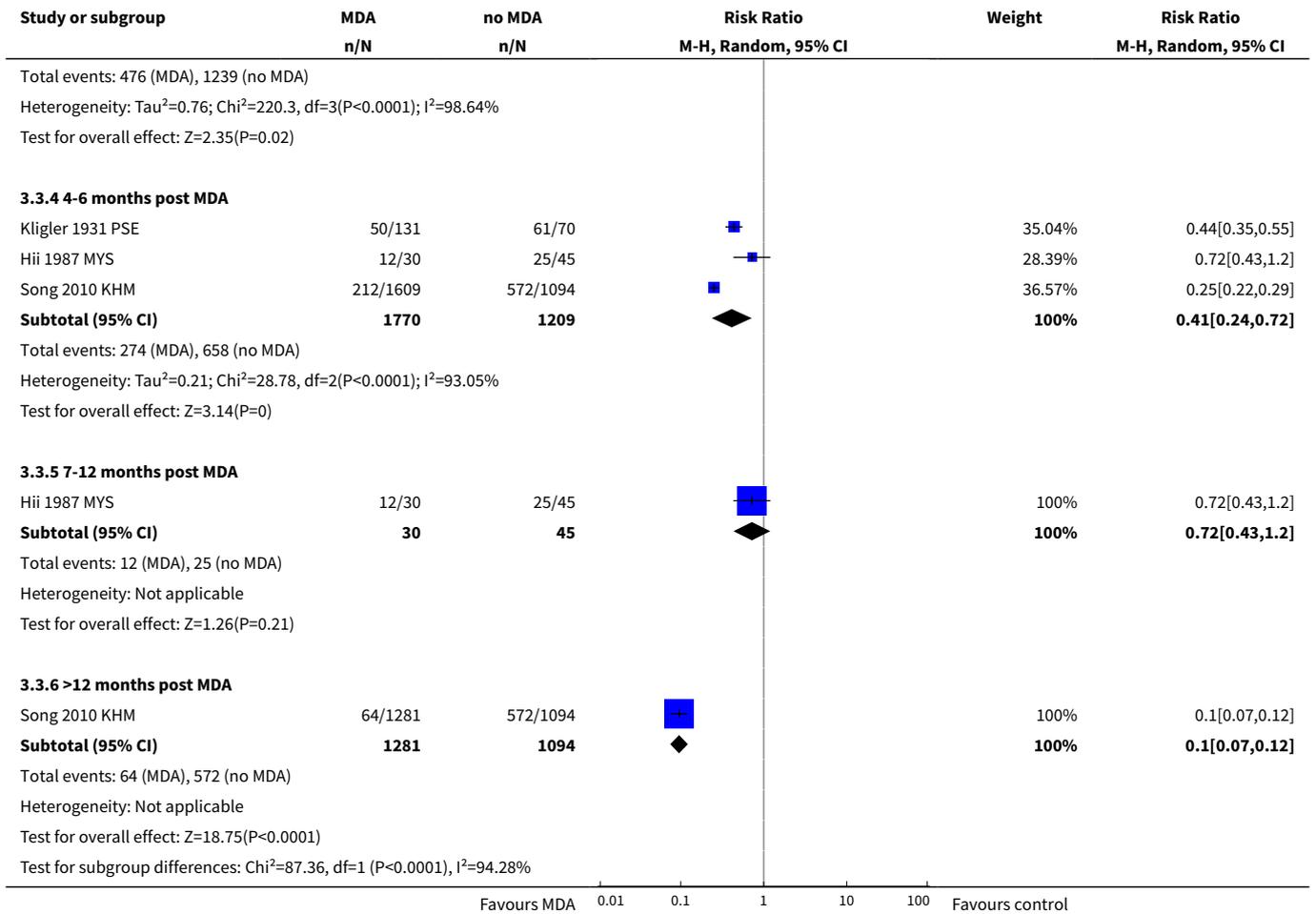
Analysis 3.2. Comparison 3 MDA versus no MDA in areas of high endemicity (Stratified by study design), Outcome 2 Parasitaemia Prevalence: Non-randomized controlled studies.



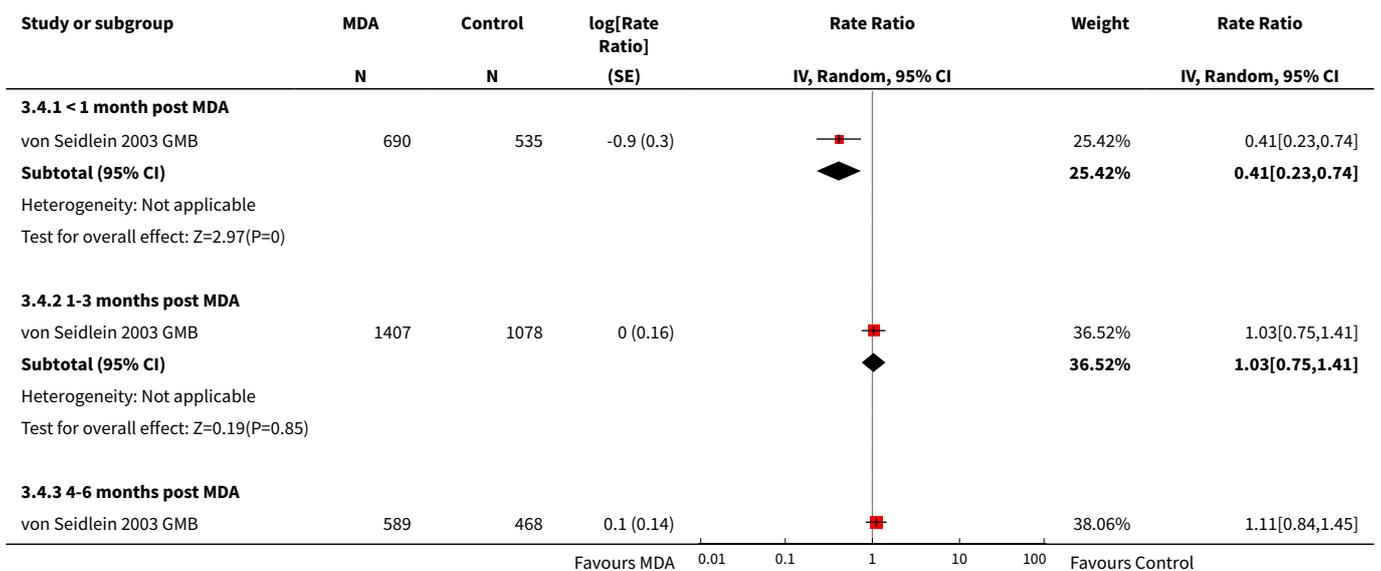


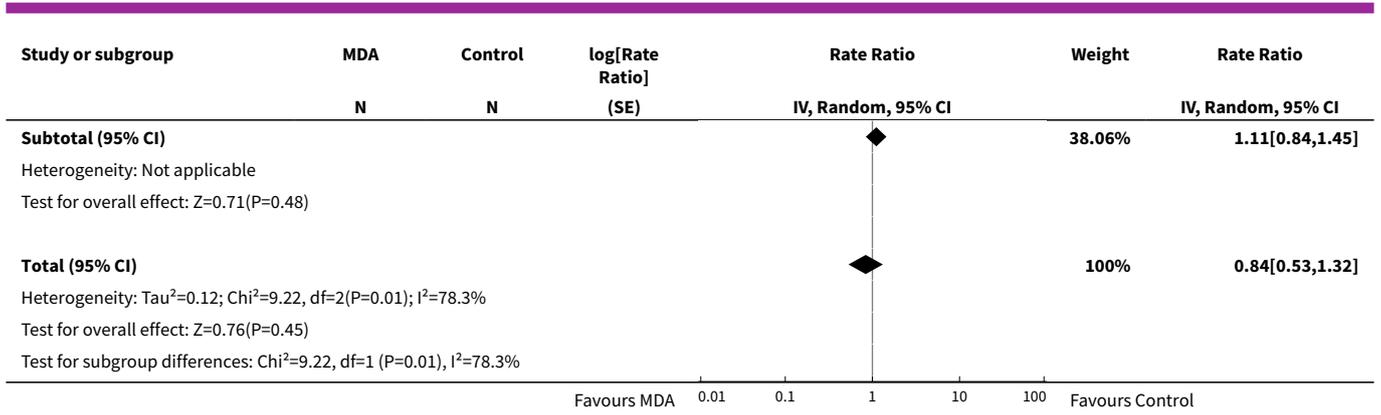
Analysis 3.3. Comparison 3 MDA versus no MDA in areas of high endemicity (Stratified by study design), Outcome 3 Parasitaemia Prevalence: Uncontrolled before-and-after studies.



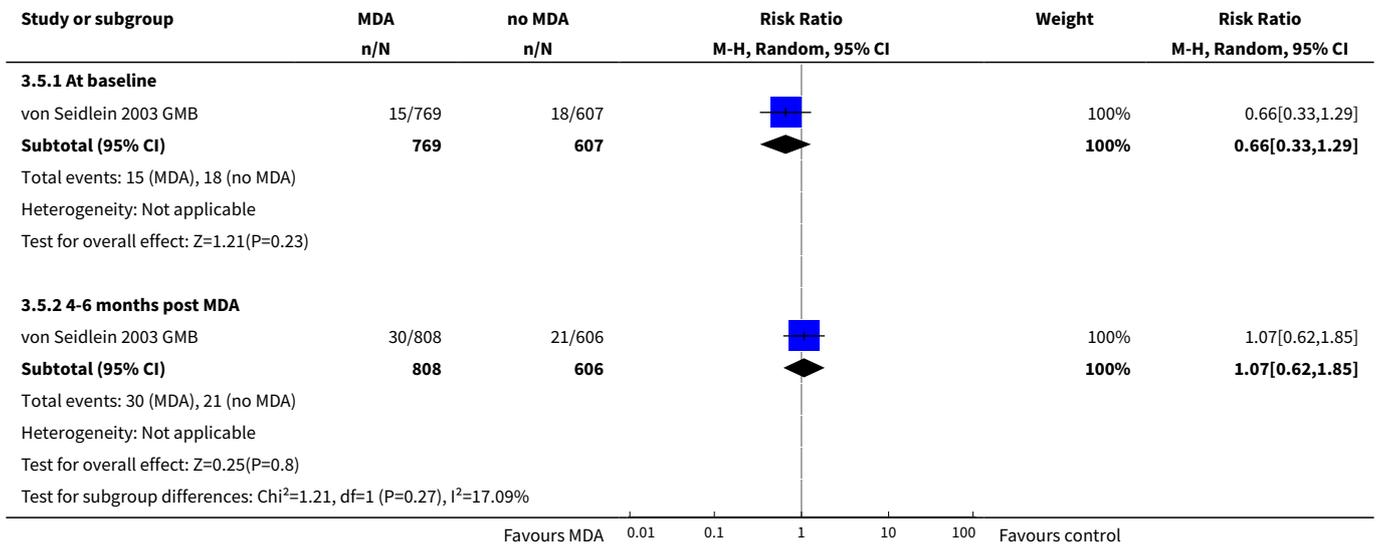


Analysis 3.4. Comparison 3 MDA versus no MDA in areas of high endemicity (Stratified by study design), Outcome 4 Parasitaemia Incidence: Cluster-randomized trials.

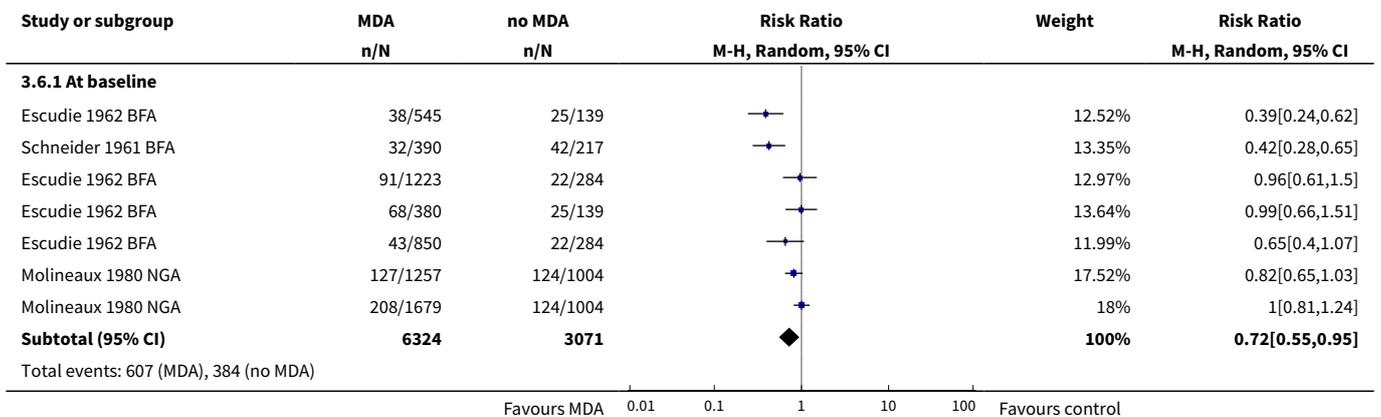


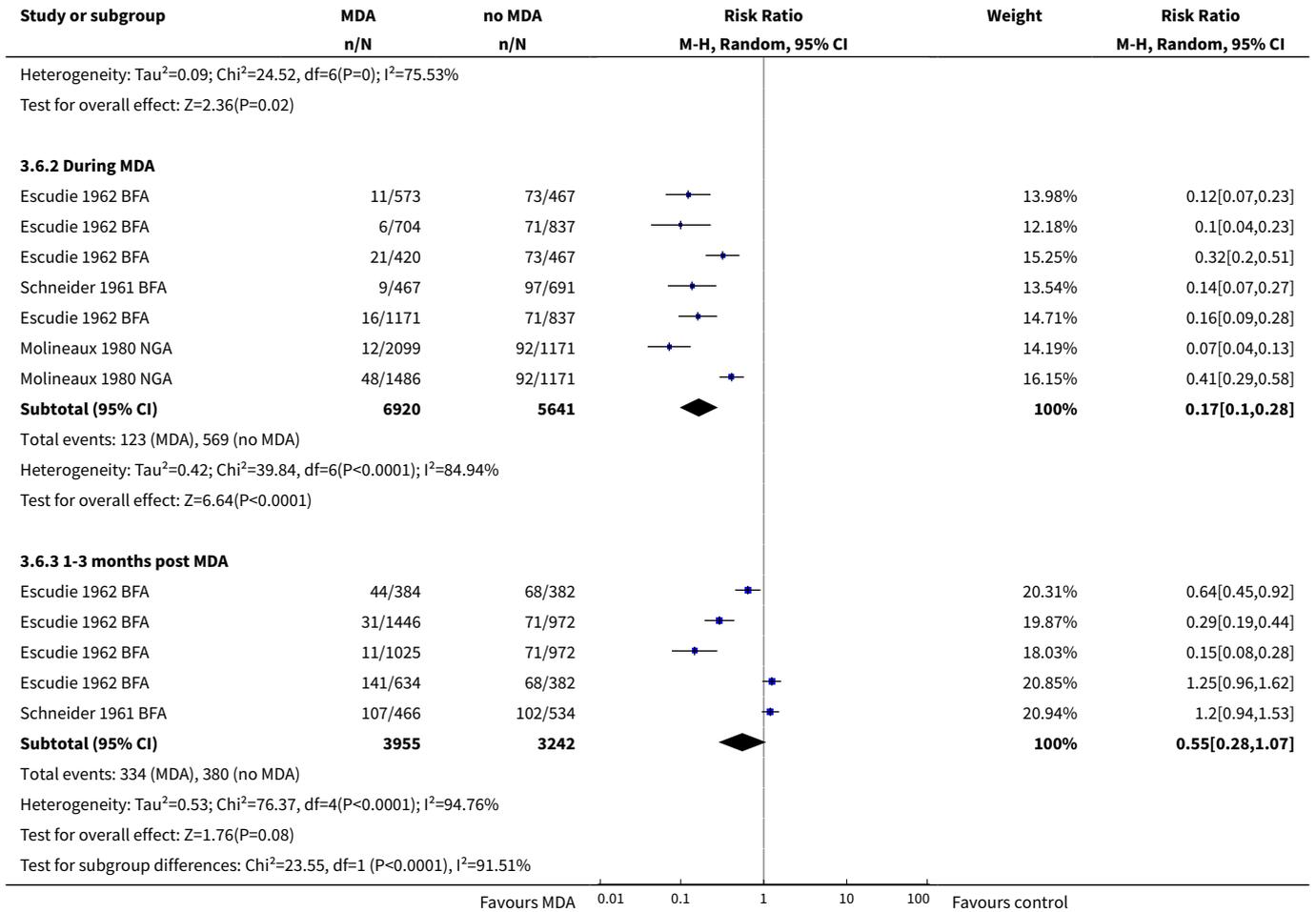


Analysis 3.5. Comparison 3 MDA versus no MDA in areas of high endemicity (Stratified by study design), Outcome 5 Gametocytaemia Prevalence: Cluster-randomized trials.

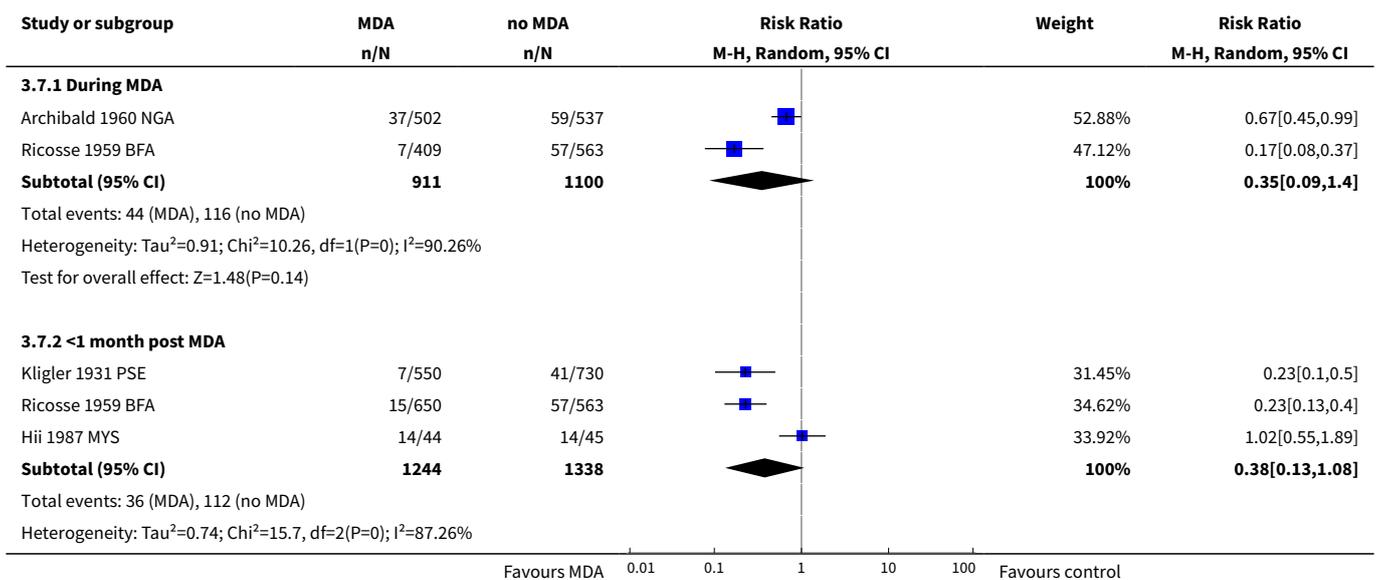


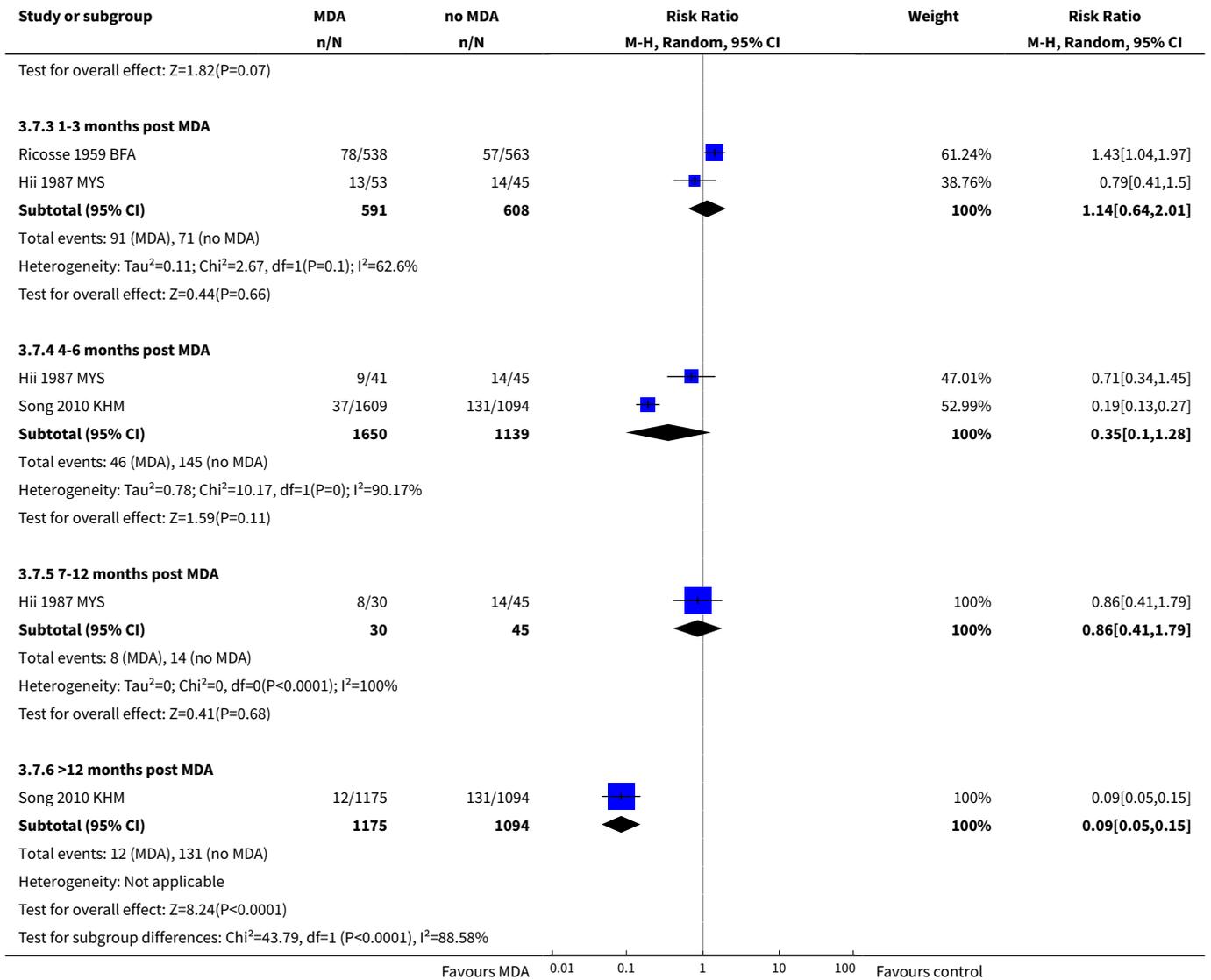
Analysis 3.6. Comparison 3 MDA versus no MDA in areas of high endemicity (Stratified by study design), Outcome 6 Gametocytaemia Prevalence: Non-randomized controlled studies.



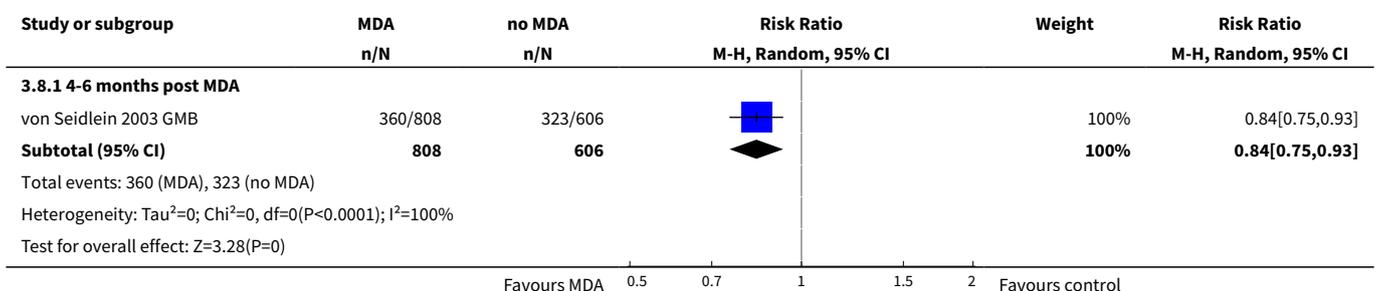


Analysis 3.7. Comparison 3 MDA versus no MDA in areas of high endemicity (Stratified by study design), Outcome 7 Gametocytaemia Prevalence: Uncontrolled before-and-after studies.

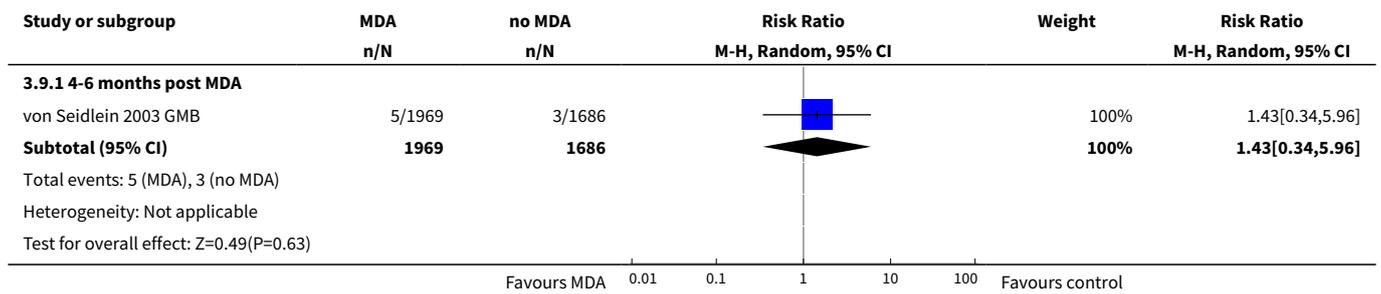




Analysis 3.8. Comparison 3 MDA versus no MDA in areas of high endemicity (Stratified by study design), Outcome 8 Anaemia Prevalence: Cluster-randomized trials.



Analysis 3.9. Comparison 3 MDA versus no MDA in areas of high endemicity (Stratified by study design), Outcome 9 Mortality: Cluster-randomized trials.

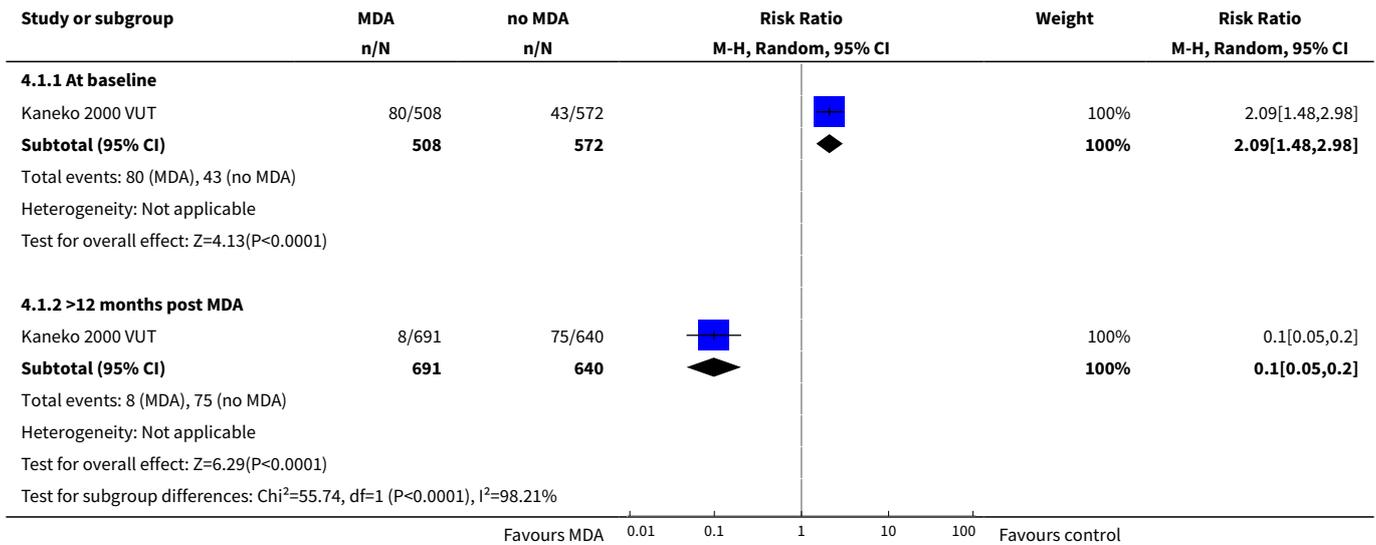


Comparison 4. MDA + vector control versus no intervention in areas of moderate endemicity (Stratified by study design)

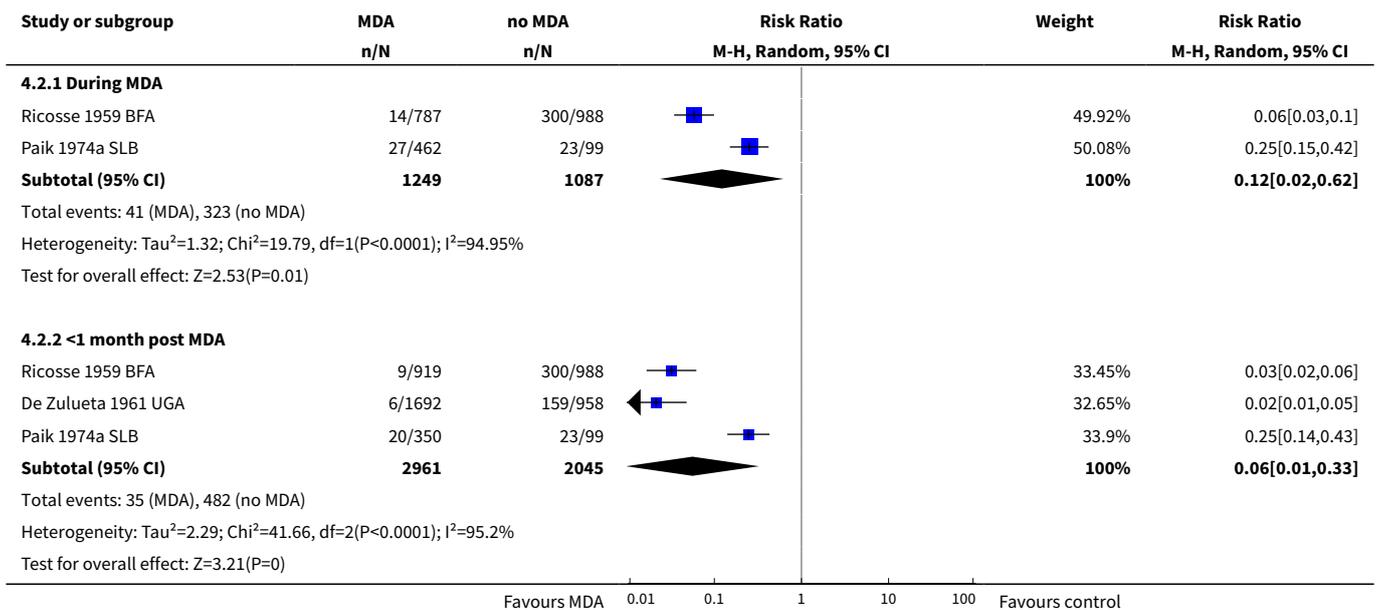
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia Prevalence: Non-randomized controlled studies	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 At baseline	1	1080	Risk Ratio (M-H, Random, 95% CI)	2.09 [1.48, 2.98]
1.2 >12 months post MDA	1	1331	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.05, 0.20]
2 Parasitaemia Prevalence: Uncontrolled before-and-after studies	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 During MDA	2	2336	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.02, 0.62]
2.2 <1 month post MDA	3	5006	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.01, 0.33]
2.3 1-3 months post MDA	3	4724	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.04, 0.57]
2.4 4-6 months post MDA	1	939	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.39, 0.85]
2.5 >12 months post MDA	1	1758	Risk Ratio (M-H, Random, 95% CI)	0.00 [0.00, 0.03]
3 Gametocytaemia Prevalence: Uncontrolled before-and-after studies	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 During MDA	2	4425	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.06, 0.27]
3.2 < 1 month post MDA	1	1907	Risk Ratio (M-H, Random, 95% CI)	0.01 [0.00, 0.16]

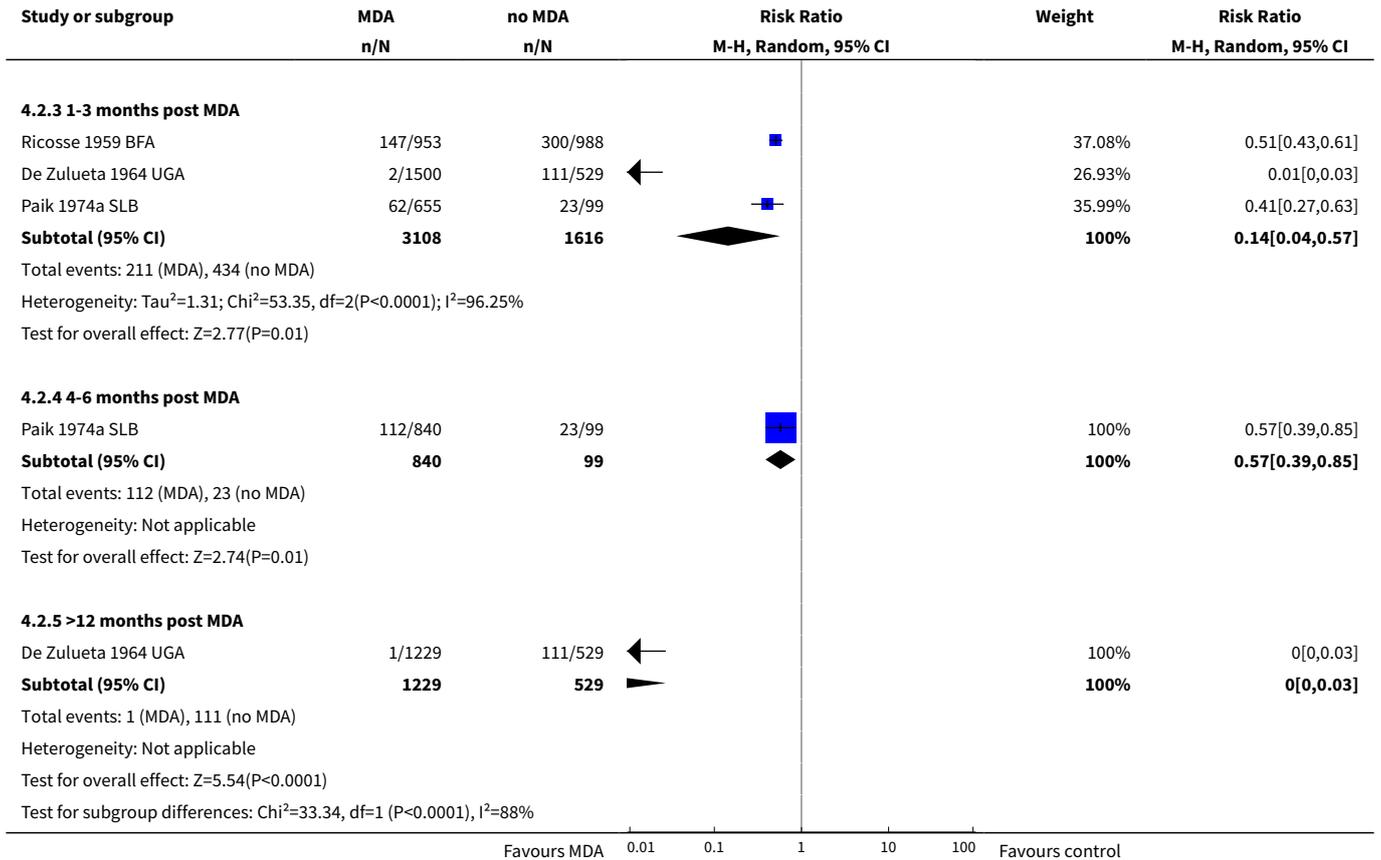
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 1-3 months post MDA	1	1941	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.11, 0.41]

Analysis 4.1. Comparison 4 MDA + vector control versus no intervention in areas of moderate endemicity (Stratified by study design), Outcome 1 Parasitaemia Prevalence: Non-randomized controlled studies.

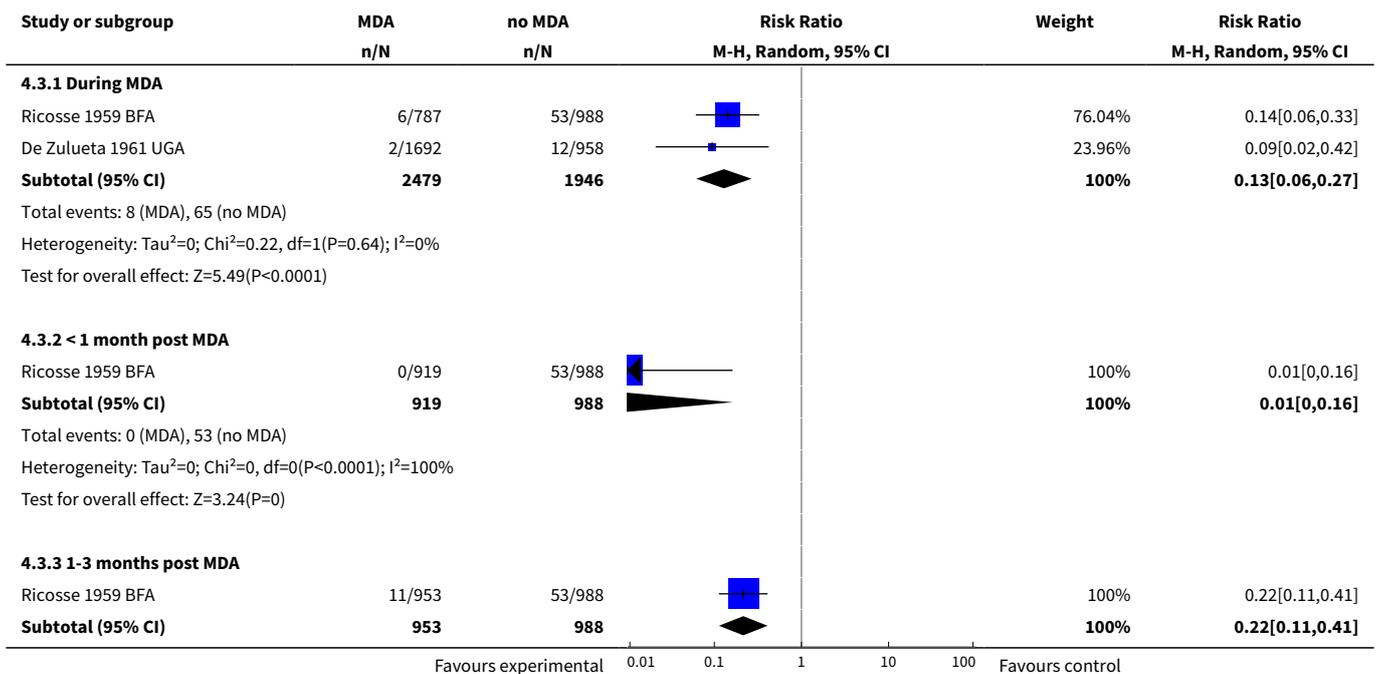


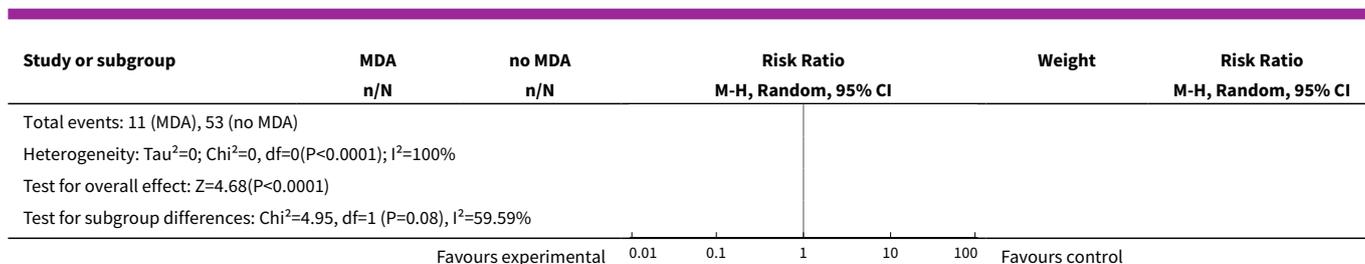
Analysis 4.2. Comparison 4 MDA + vector control versus no intervention in areas of moderate endemicity (Stratified by study design), Outcome 2 Parasitaemia Prevalence: Uncontrolled before-and-after studies.





Analysis 4.3. Comparison 4 MDA + vector control versus no intervention in areas of moderate endemicity (Stratified by study design), Outcome 3 Gametocytaemia Prevalence: Uncontrolled before-and-after studies.



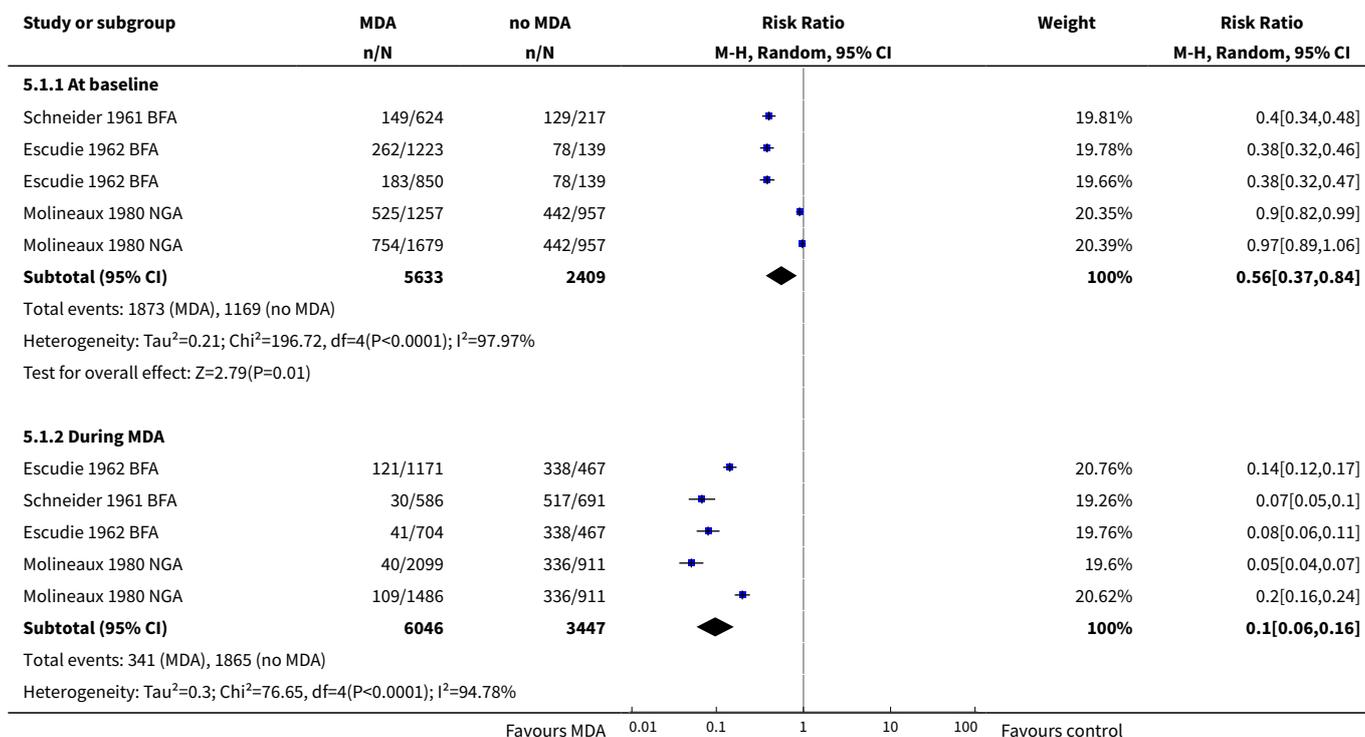


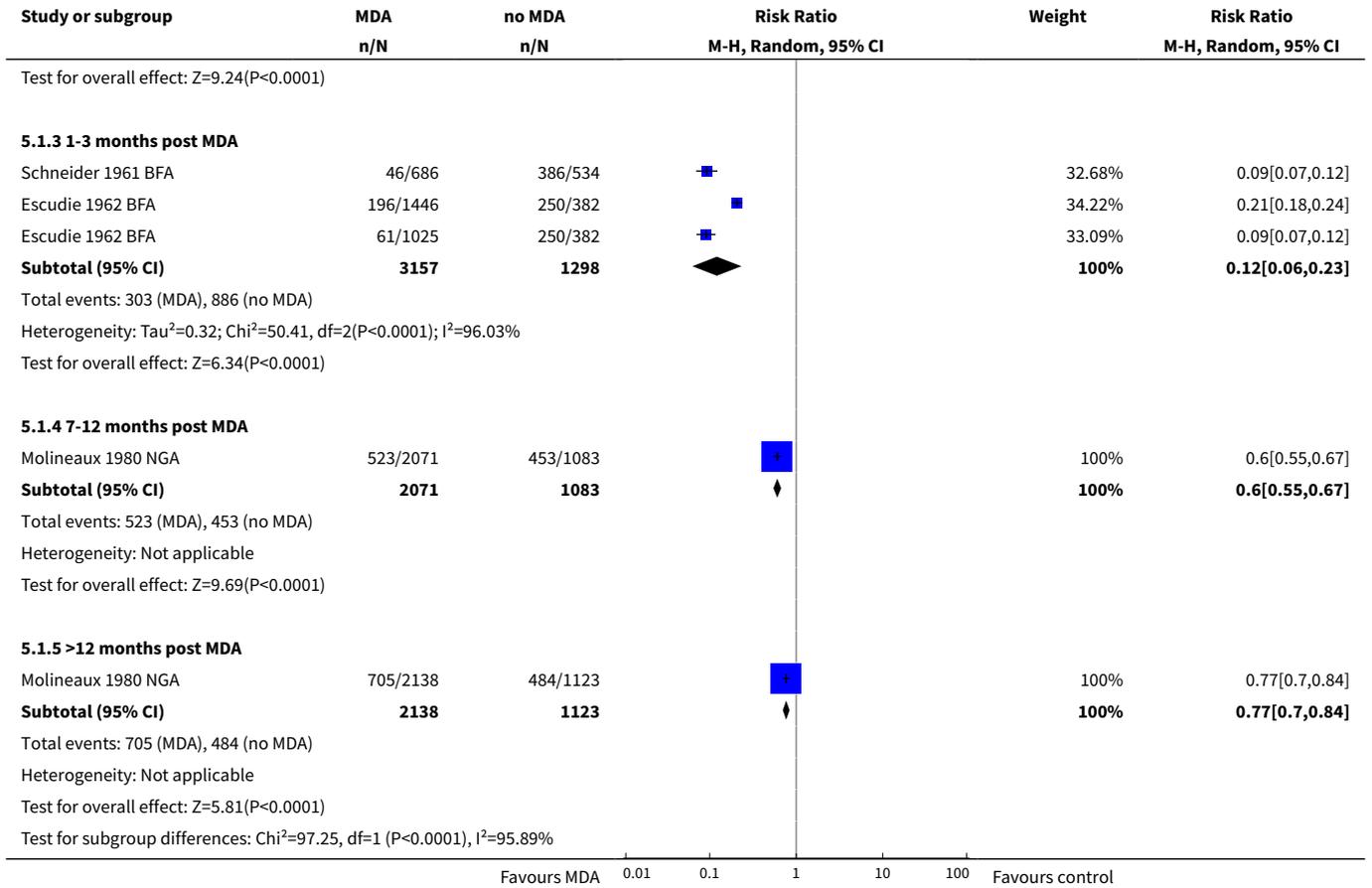
Comparison 5. MDA + vector control versus no intervention in areas of high endemicity (Stratified by study design)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia Prevalence: Non-randomized controlled studies	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 At baseline	3	8042	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.37, 0.84]
1.2 During MDA	3	9493	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.06, 0.16]
1.3 1-3 months post MDA	2	4455	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.06, 0.23]
1.4 7-12 months post MDA	1	3154	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.55, 0.67]
1.5 >12 months post MDA	1	3261	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.70, 0.84]
2 Parasitaemia Prevalence: Uncontrolled before-and-after studies	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 During MDA	2	5437	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.09, 0.31]
2.2 1-3 months post MDA	2	5440	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.51]
2.3 4-6 months post MDA	1	415	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.66, 1.04]
2.4 7-12 months post MDA	1	412	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.16]
3 Gametocyaemia Prevalence: Non-randomized controlled studies	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 At baseline	3	8042	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.31, 0.90]
3.2 During MDA	3	9493	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.03, 0.20]

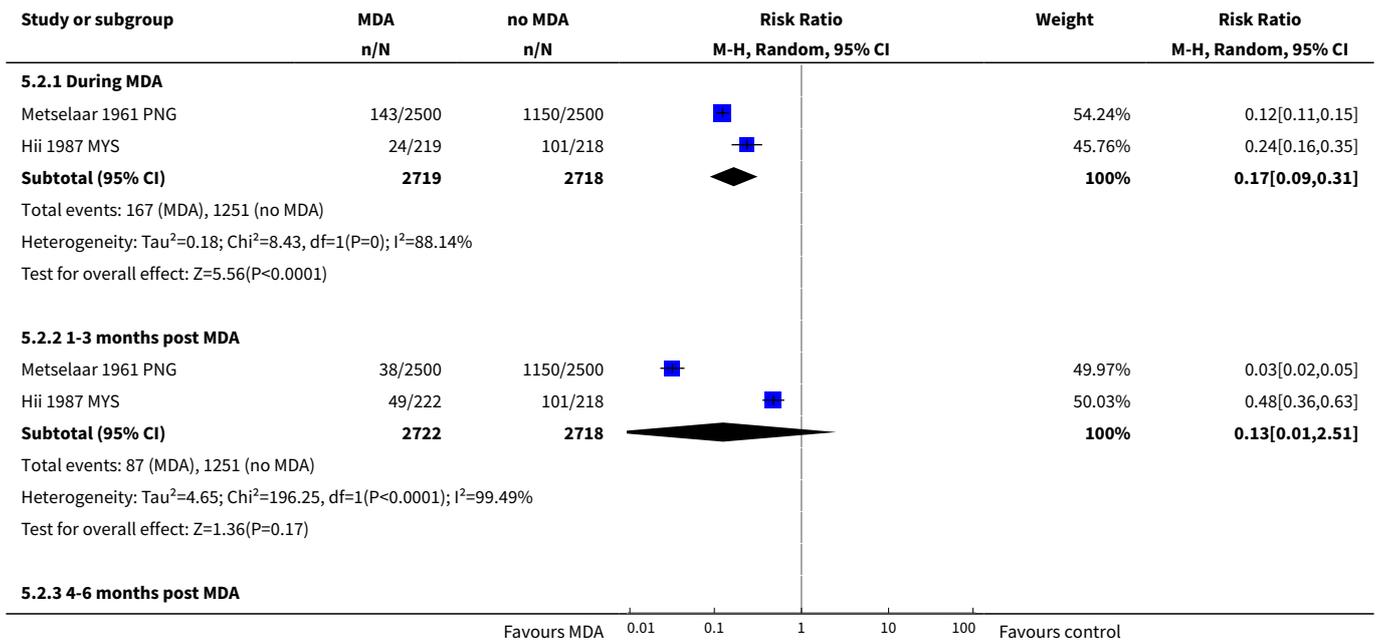
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 1-3 months post MDA	2	4455	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.05, 0.14]
3.4 7-12 months post MDA	1	3154	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.73, 1.05]
3.5 > 12 months post MDA	1	3261	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.81, 1.14]
4 Gametocytaemia Prevalence: Uncontrolled before-and-after studies	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 During MDA	1	437	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.17, 0.50]
4.2 1-3 months post MDA	1	440	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.34, 0.80]
4.3 4-6 months post MDA	1	415	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.52, 1.12]
4.4 7-12 months post MDA	1	412	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.65, 1.33]

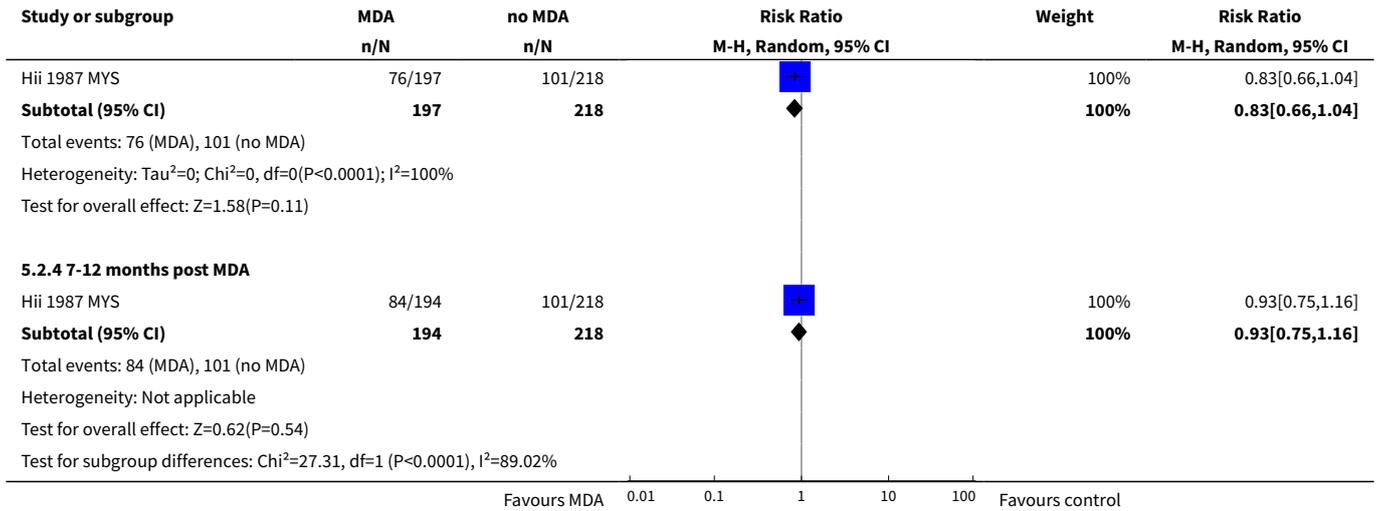
Analysis 5.1. Comparison 5 MDA + vector control versus no intervention in areas of high endemicity (Stratified by study design), Outcome 1 Parasitaemia Prevalence: Non-randomized controlled studies.



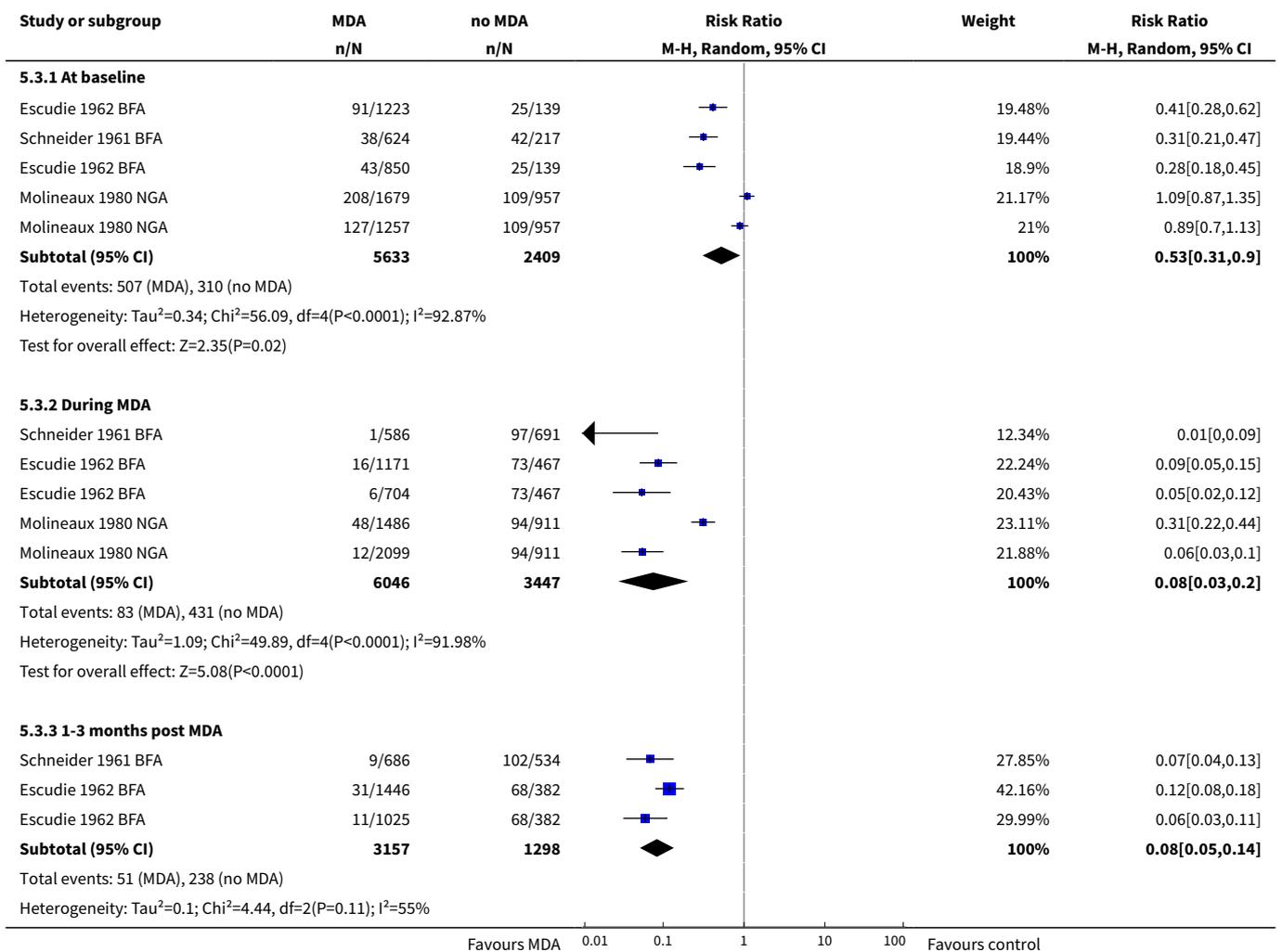


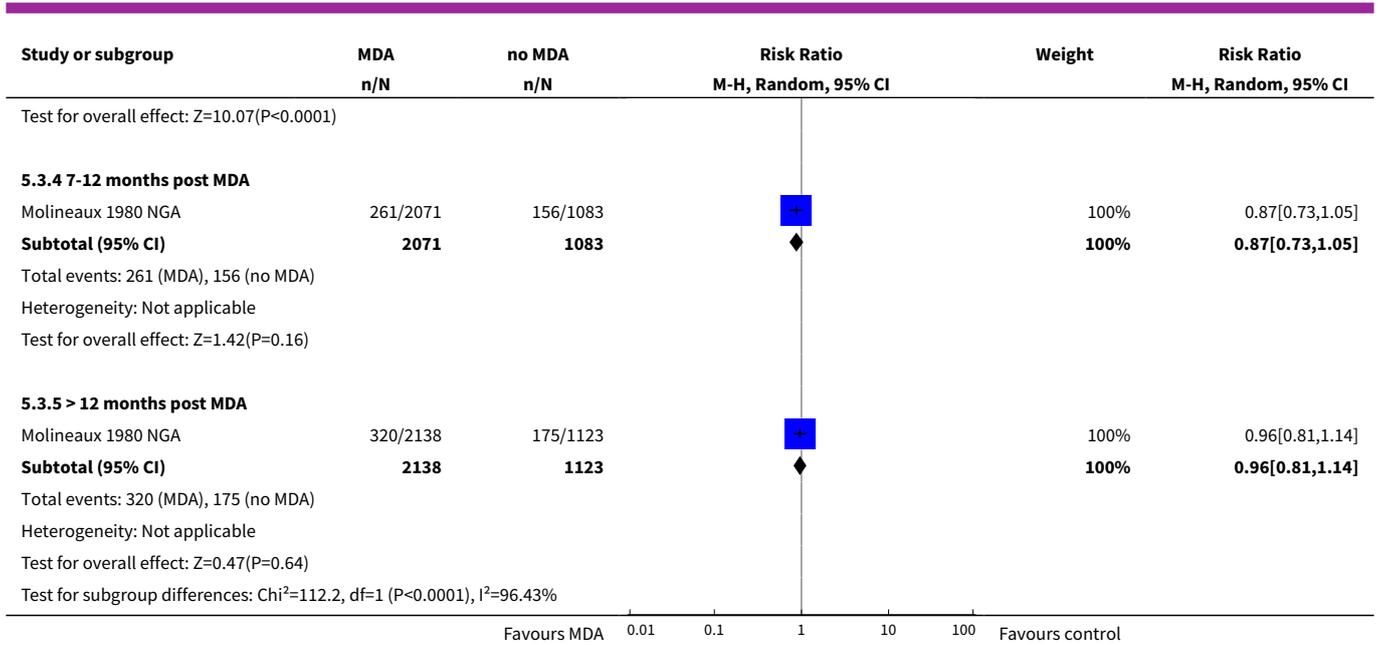
Analysis 5.2. Comparison 5 MDA + vector control versus no intervention in areas of high endemicity (Stratified by study design), Outcome 2 Parasitaemia Prevalence: Uncontrolled before-and-after studies.



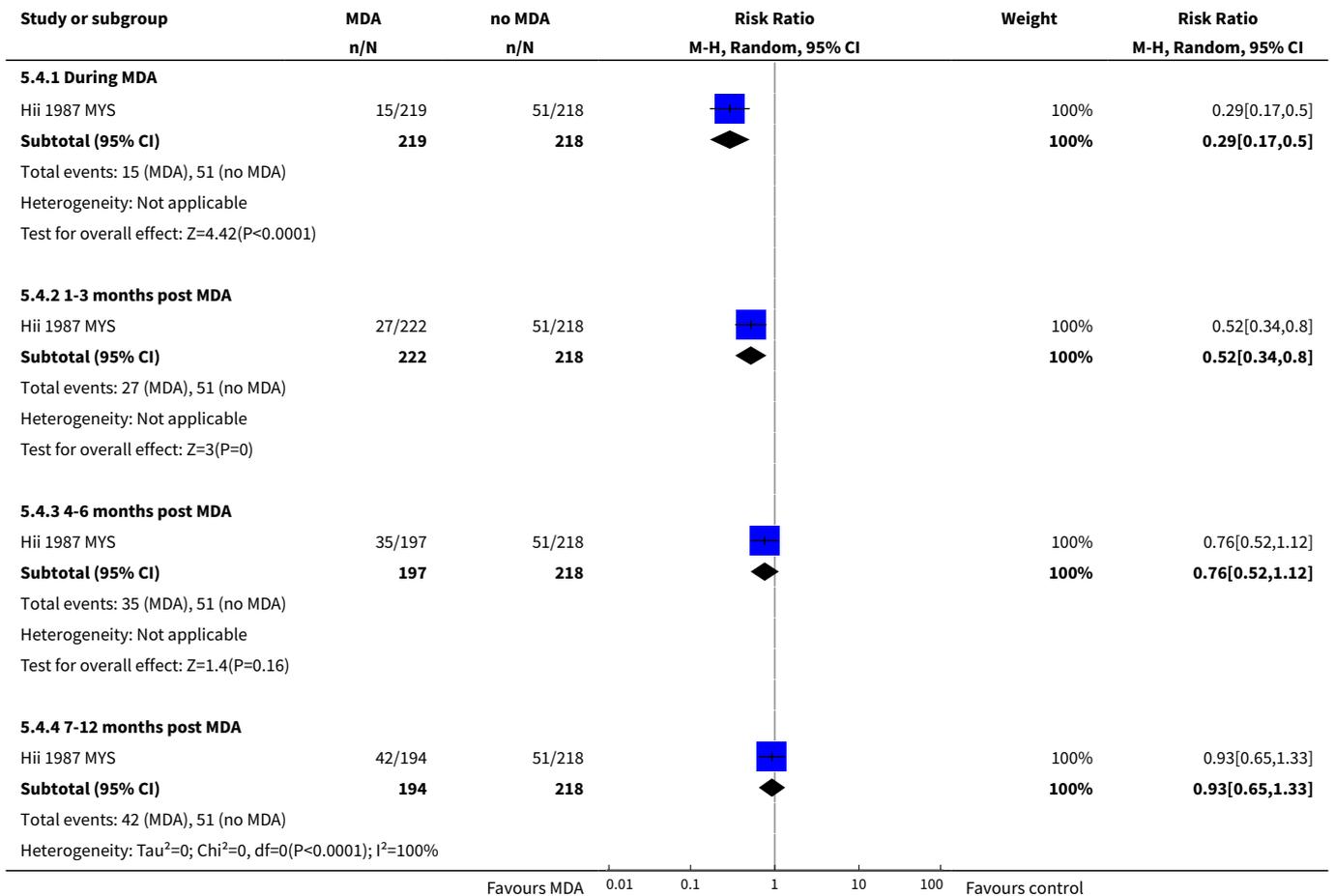


Analysis 5.3. Comparison 5 MDA + vector control versus no intervention in areas of high endemicity (Stratified by study design), Outcome 3 Gametocytaemia Prevalence: Non-randomized controlled studies.





Analysis 5.4. Comparison 5 MDA + vector control versus no intervention in areas of high endemicity (Stratified by study design), Outcome 4 Gametocytaemia Prevalence: Uncontrolled before-and-after studies.

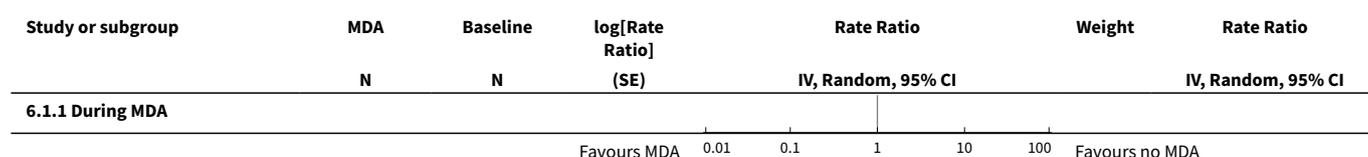


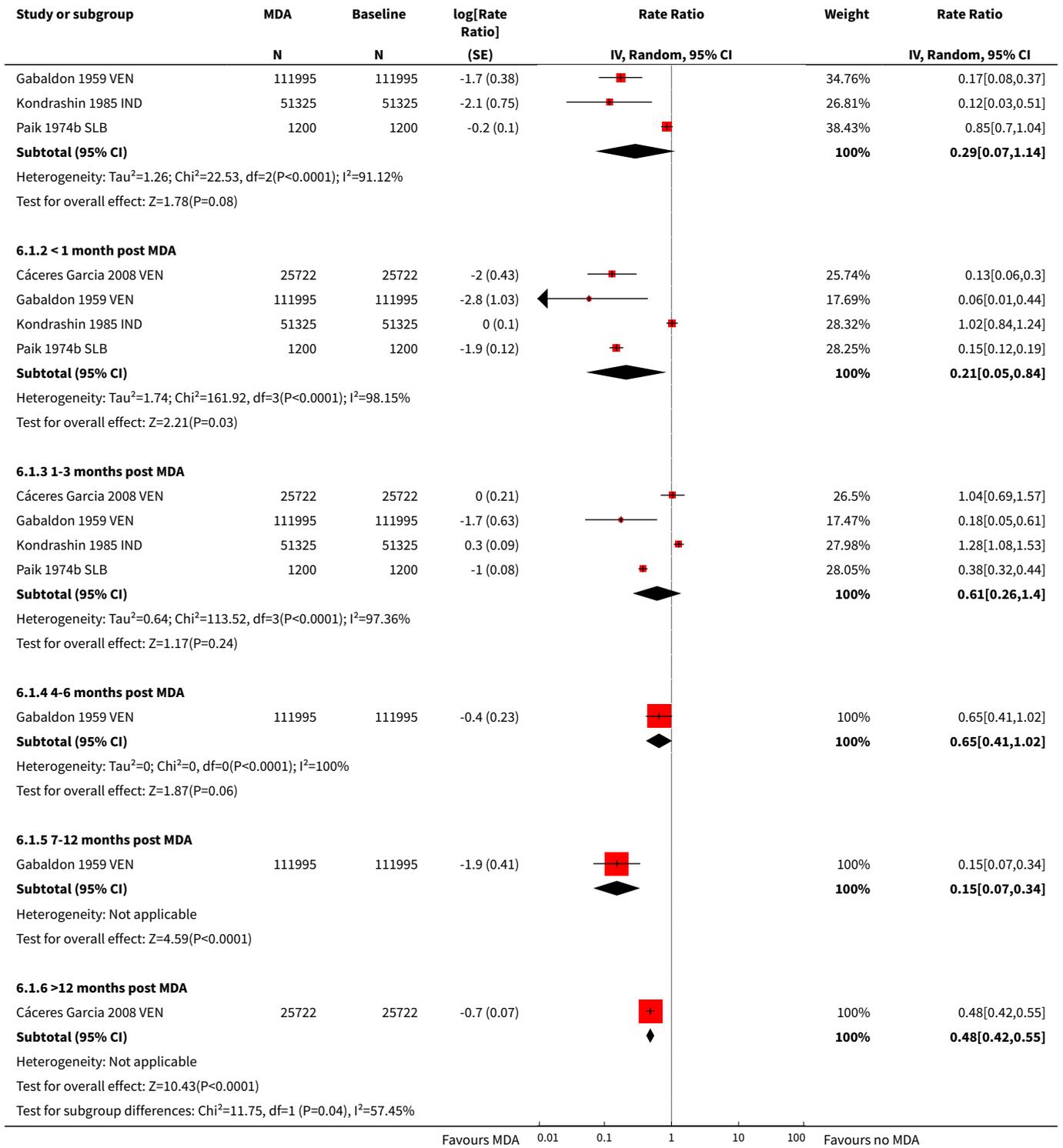


Comparison 6. Parasitaemia Incidence studies

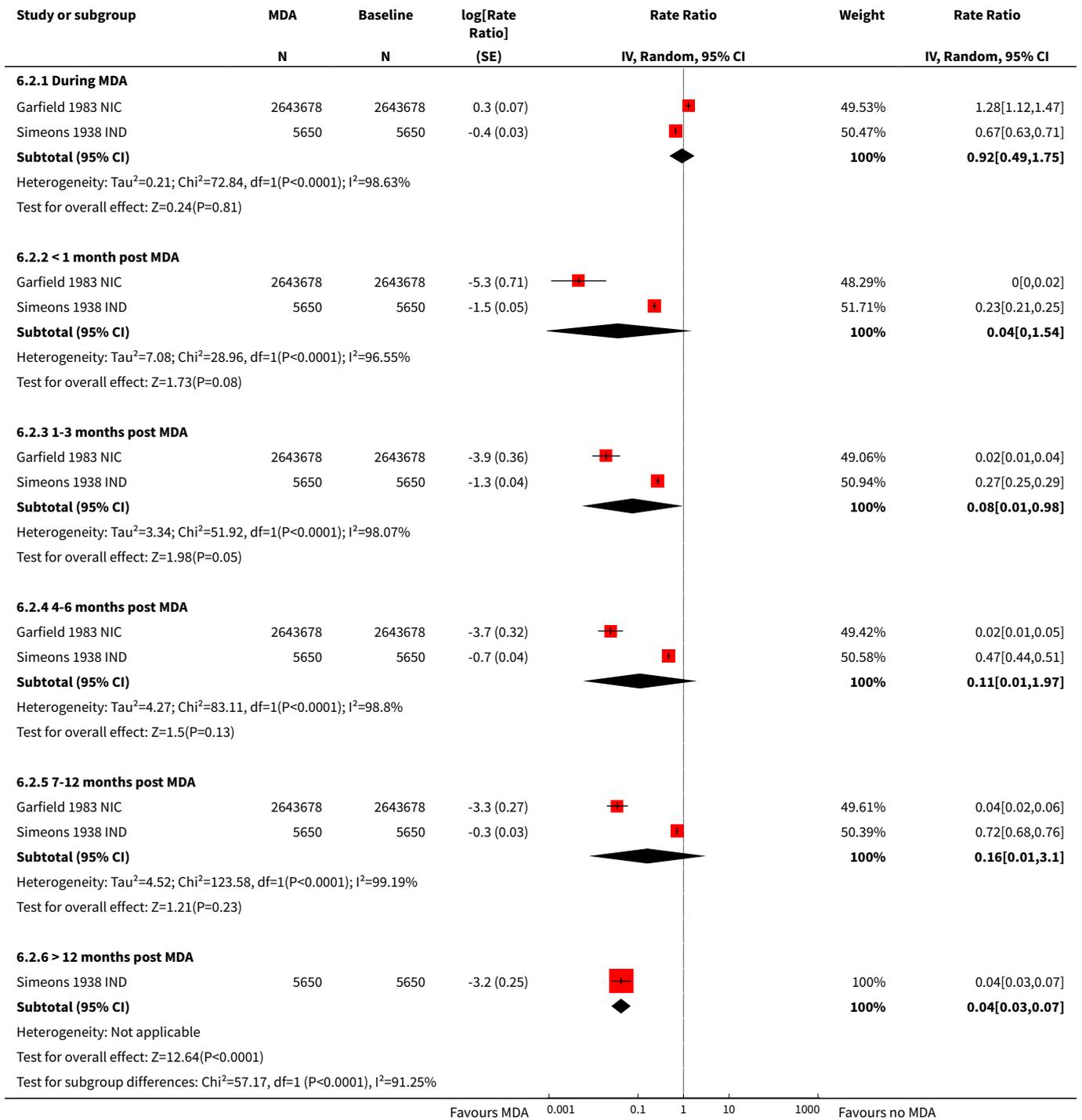
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 MDA versus no MDA: Uncontrolled before-and-after studies	4		Rate Ratio (Random, 95% CI)	Subtotals only
1.1 During MDA	3		Rate Ratio (Random, 95% CI)	0.29 [0.07, 1.14]
1.2 < 1 month post MDA	4		Rate Ratio (Random, 95% CI)	0.21 [0.05, 0.84]
1.3 1-3 months post MDA	4		Rate Ratio (Random, 95% CI)	0.61 [0.26, 1.40]
1.4 4-6 months post MDA	1		Rate Ratio (Random, 95% CI)	0.65 [0.41, 1.02]
1.5 7-12 months post MDA	1		Rate Ratio (Random, 95% CI)	0.15 [0.07, 0.34]
1.6 >12 months post MDA	1		Rate Ratio (Random, 95% CI)	0.48 [0.42, 0.55]
2 MDA + vector control versus no MDA: Uncontrolled before-and-after studies	2		Rate Ratio (Random, 95% CI)	Subtotals only
2.1 During MDA	2		Rate Ratio (Random, 95% CI)	0.92 [0.49, 1.75]
2.2 < 1 month post MDA	2		Rate Ratio (Random, 95% CI)	0.04 [0.00, 1.54]
2.3 1-3 months post MDA	2		Rate Ratio (Random, 95% CI)	0.08 [0.01, 0.98]
2.4 4-6 months post MDA	2		Rate Ratio (Random, 95% CI)	0.11 [0.01, 1.97]
2.5 7-12 months post MDA	2		Rate Ratio (Random, 95% CI)	0.16 [0.01, 3.10]
2.6 > 12 months post MDA	1		Rate Ratio (Random, 95% CI)	0.04 [0.03, 0.07]

Analysis 6.1. Comparison 6 Parasitaemia Incidence studies, Outcome 1 MDA versus no MDA: Uncontrolled before-and-after studies.





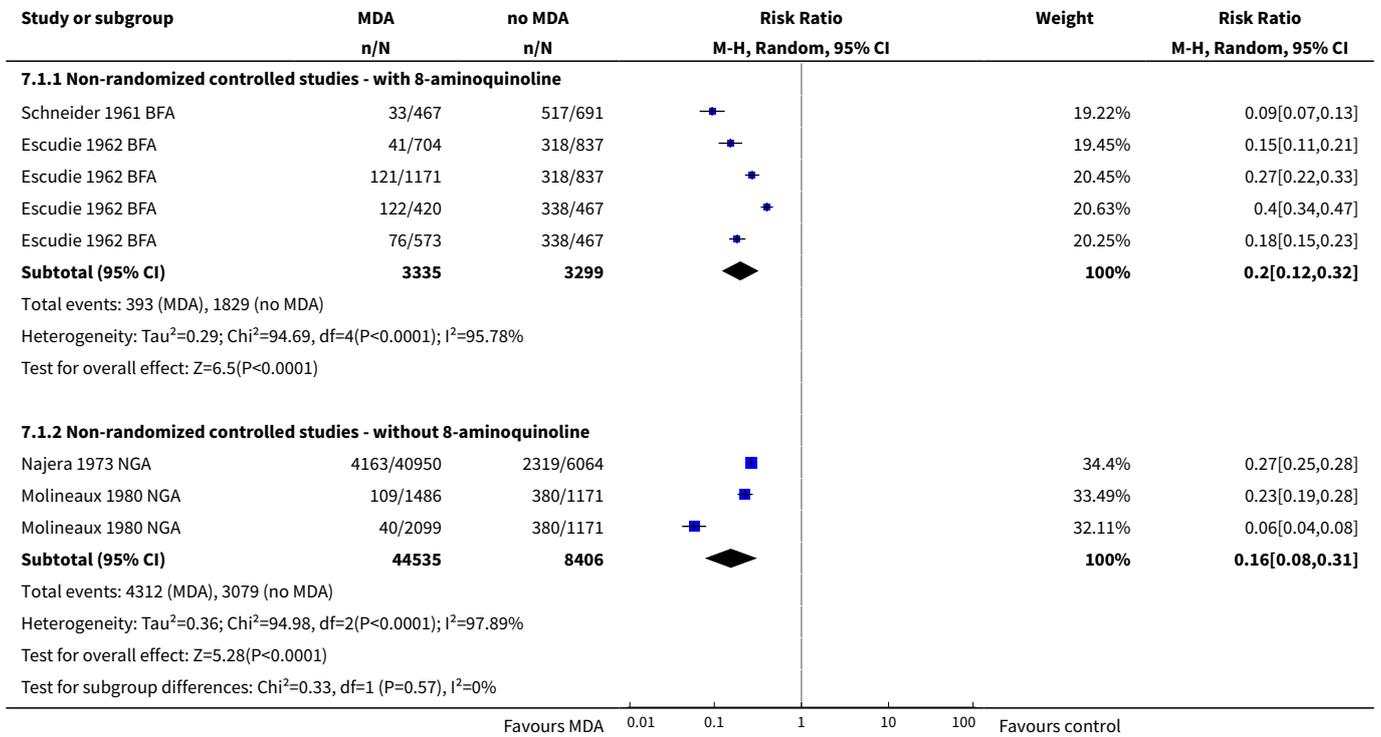
**Analysis 6.2. Comparison 6 Parasitaemia Incidence studies, Outcome 2
MDA + vector control versus no MDA: Uncontrolled before-and-after studies.**



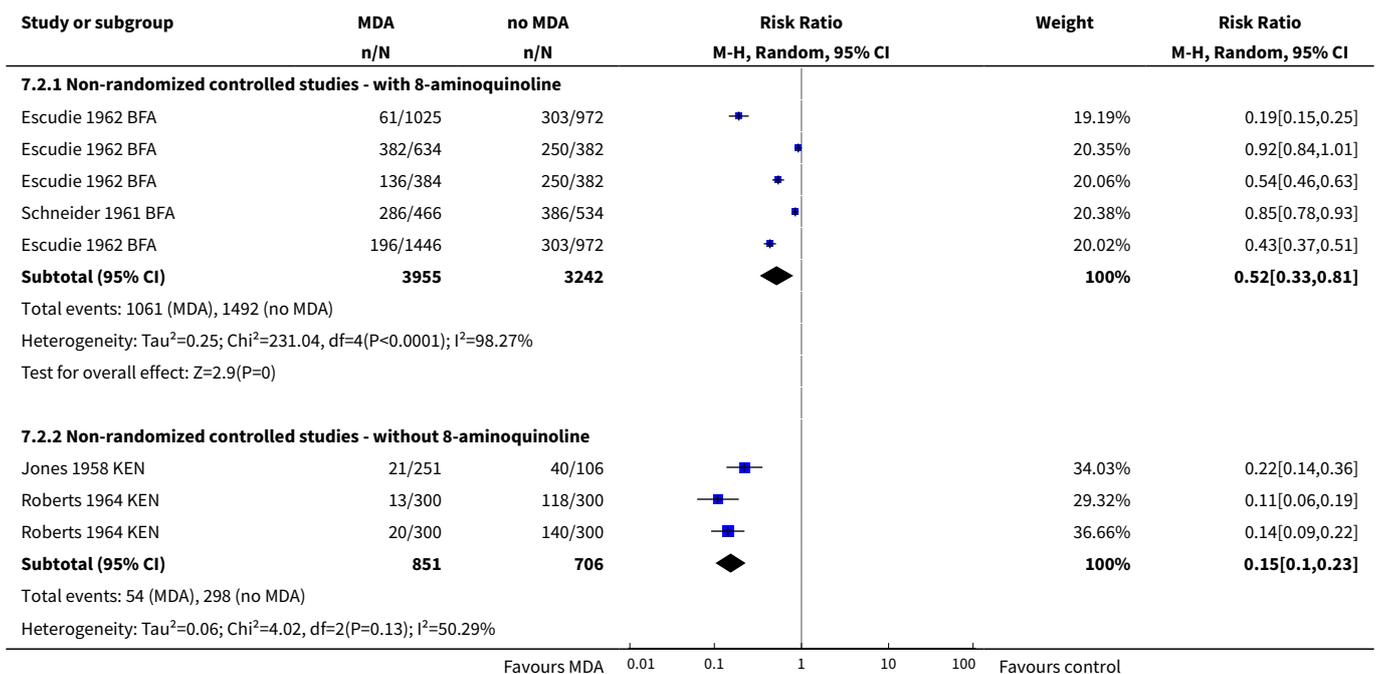
Comparison 7. MDA versus no MDA in areas of moderate and high endemicity (Stratified by study design; subgrouped by 8-aminoquinoline)

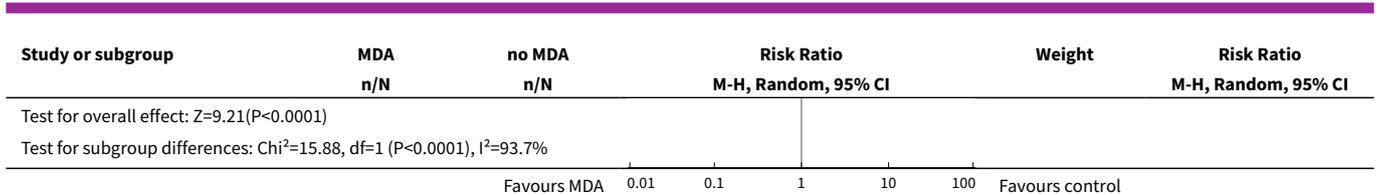
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia Prevalence during MDA	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Non-randomized controlled studies - with 8-aminoquinoline	2	6634	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.12, 0.32]
1.2 Non-randomized controlled studies - without 8-aminoquinoline	2	52941	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.08, 0.31]
2 Parasitaemia Prevalence 1-3 months post MDA	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Non-randomized controlled studies - with 8-aminoquinoline	2	7197	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.33, 0.81]
2.2 Non-randomized controlled studies - without 8-aminoquinoline	2	1557	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.10, 0.23]
3 Parasitaemia Prevalence during MDA	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Uncontrolled before-and-after studies - with 8-aminoquinoline	1	2965	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.03, 0.10]
3.2 Uncontrolled before-and-after studies - without 8-aminoquinoline	3	7011	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.06, 0.51]
4 Parasitaemia Prevalence <1 month post MDA	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Uncontrolled before-and-after studies - with 8-aminoquinoline	3	2650	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.29, 0.61]
4.2 Uncontrolled before-and-after studies - without 8-aminoquinoline	4	4309	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.22, 0.38]
5 Parasitaemia Prevalence 1-3 months post MDA	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Uncontrolled before-and-after studies - with 8-aminoquinoline	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.41, 1.01]
5.2 Uncontrolled before-and-after studies - without 8-aminoquinoline	6	12959	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.29, 0.34]
6 Parasitaemia Prevalence 4-6 months post MDA	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Uncontrolled before-and-after studies - with 8-aminoquinoline	3	2979	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.24, 0.72]
6.2 Uncontrolled before-and-after studies - without 8-aminoquinoline	2	3797	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.41, 7.41]

Analysis 7.1. Comparison 7 MDA versus no MDA in areas of moderate and high endemicity (Stratified by study design; subgrouped by 8-aminoquinoline), Outcome 1 Parasitaemia Prevalence during MDA.

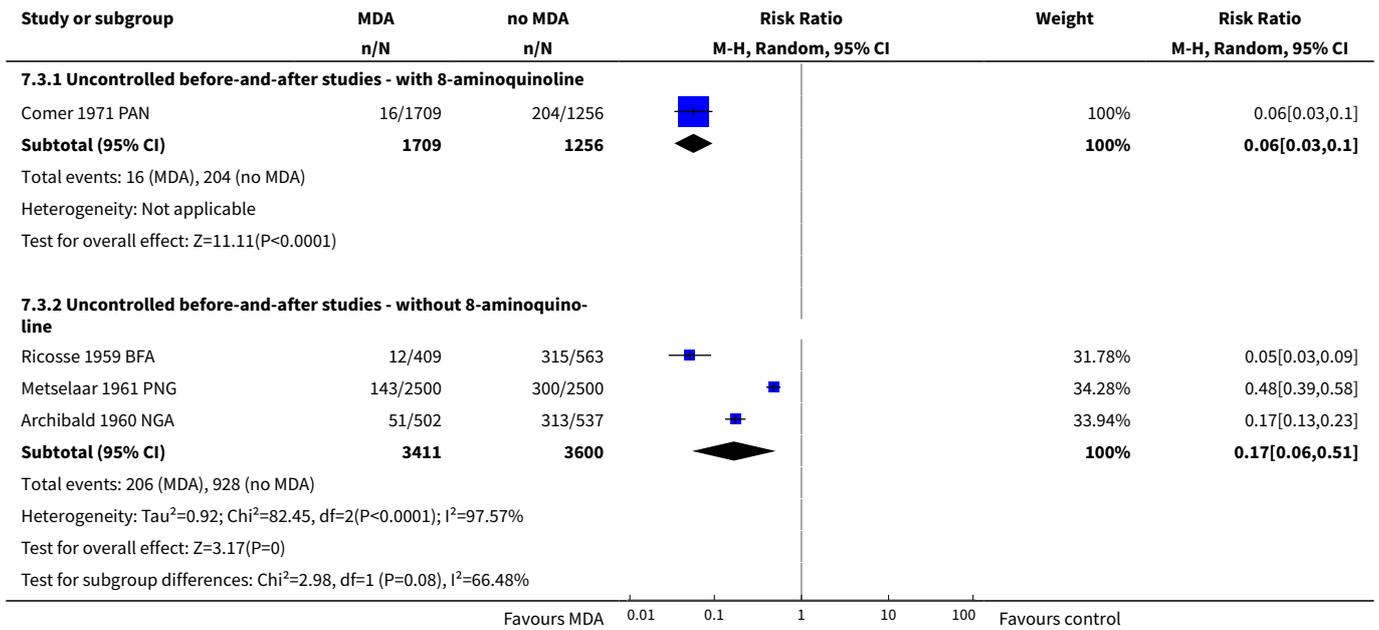


Analysis 7.2. Comparison 7 MDA versus no MDA in areas of moderate and high endemicity (Stratified by study design; subgrouped by 8-aminoquinoline), Outcome 2 Parasitaemia Prevalence 1-3 months post MDA.

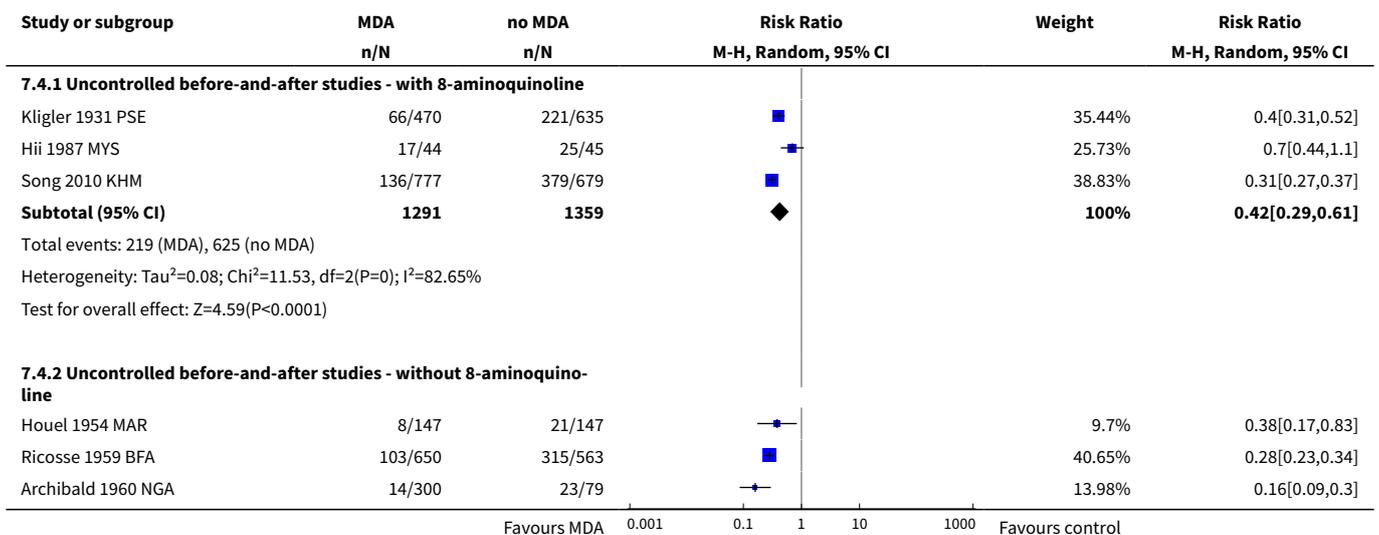


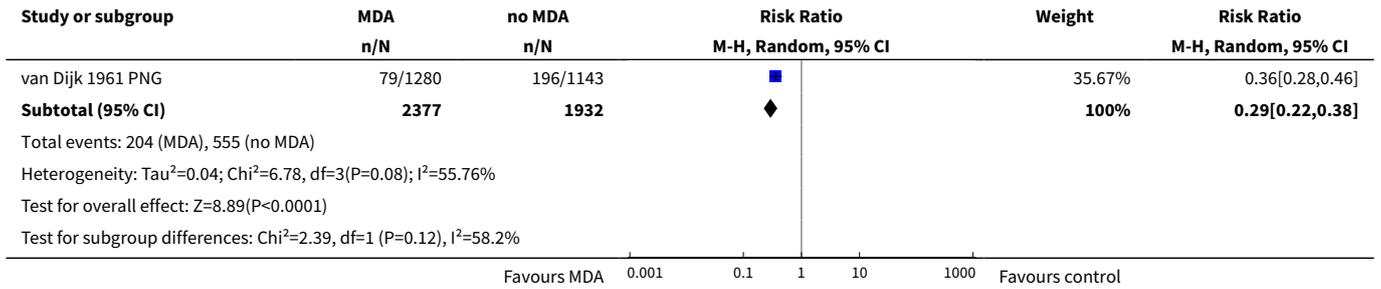


Analysis 7.3. Comparison 7 MDA versus no MDA in areas of moderate and high endemicity (Stratified by study design; subgrouped by 8-aminoquinoline), Outcome 3 Parasitaemia Prevalence during MDA.

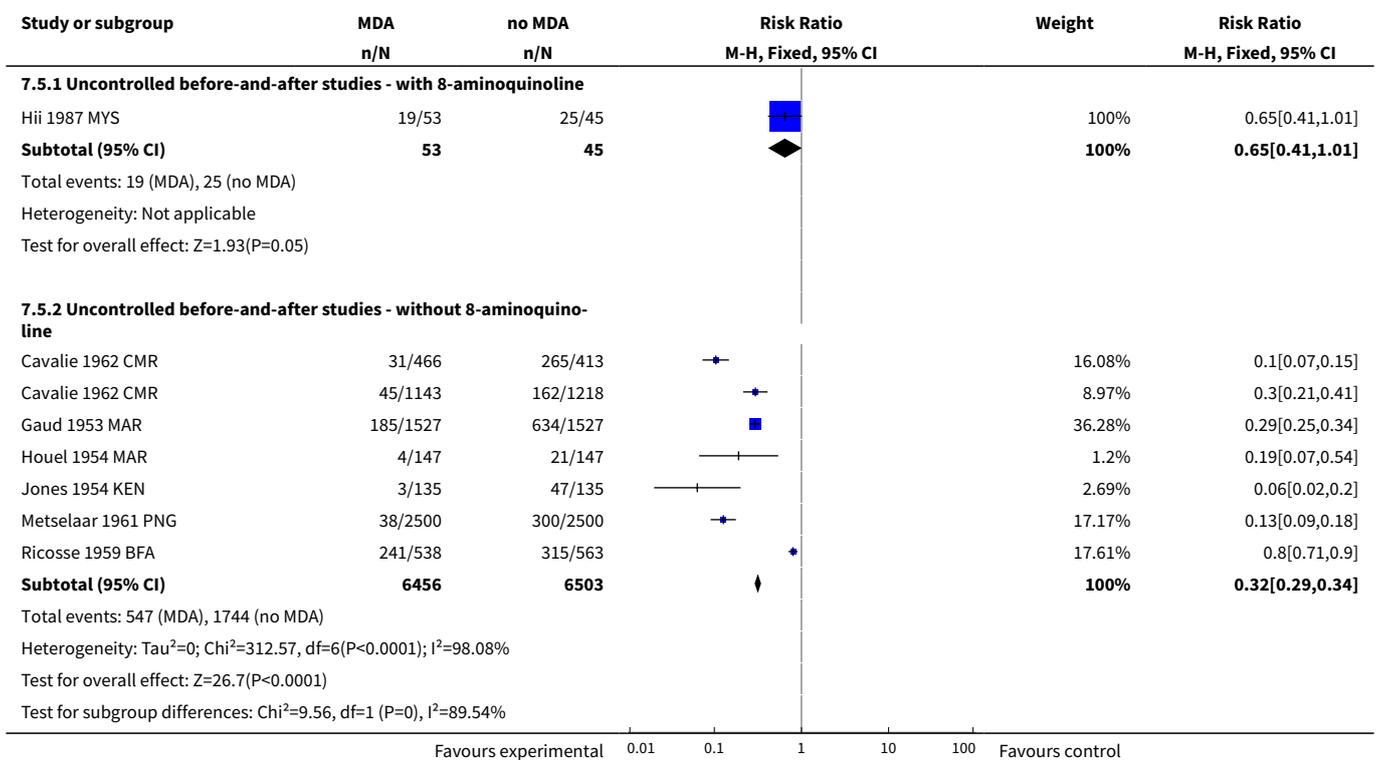


Analysis 7.4. Comparison 7 MDA versus no MDA in areas of moderate and high endemicity (Stratified by study design; subgrouped by 8-aminoquinoline), Outcome 4 Parasitaemia Prevalence <1 month post MDA.

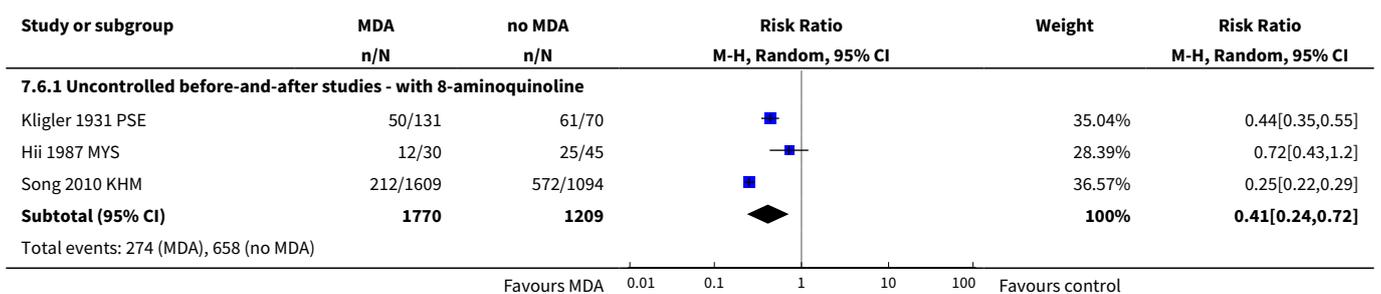


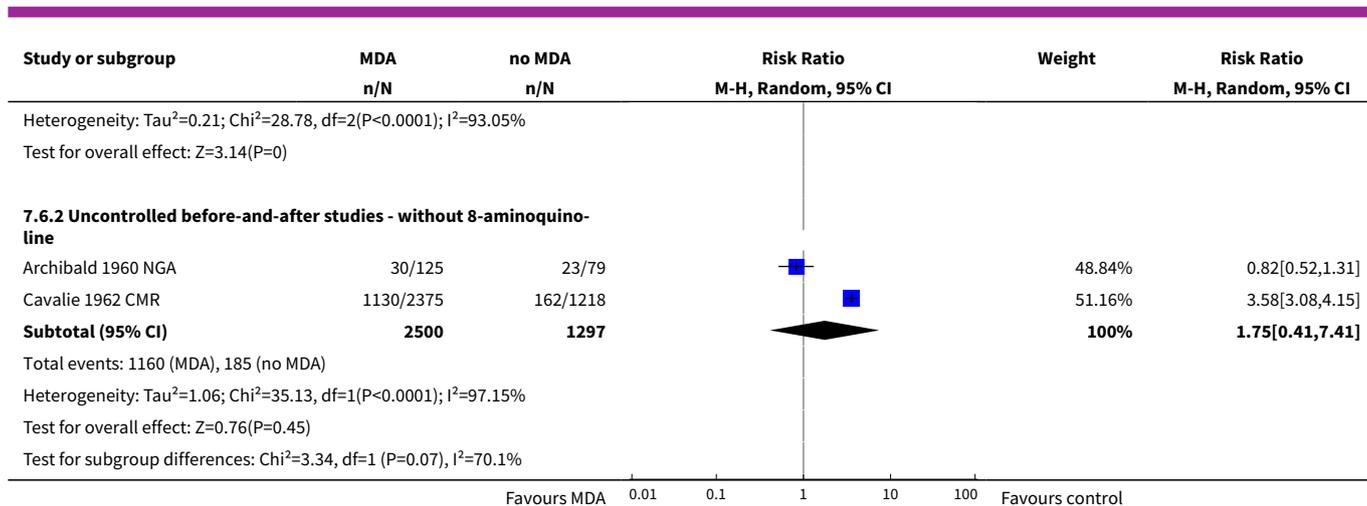


Analysis 7.5. Comparison 7 MDA versus no MDA in areas of moderate and high endemicity (Stratified by study design; subgrouped by 8-aminoquinoline), Outcome 5 Parasitaemia Prevalence 1-3 months post MDA.



Analysis 7.6. Comparison 7 MDA versus no MDA in areas of moderate and high endemicity (Stratified by study design; subgrouped by 8-aminoquinoline), Outcome 6 Parasitaemia Prevalence 4-6 months post MDA.



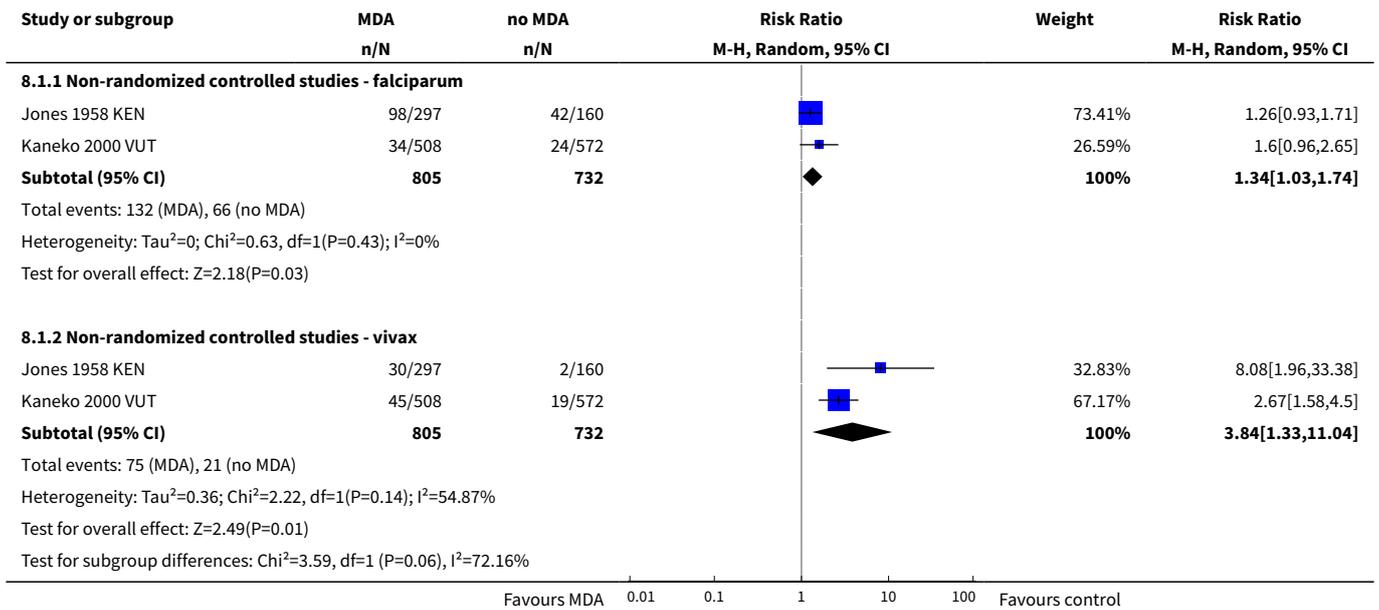


Comparison 8. MDA versus no MDA for all endemicity levels (Stratified by study design; subgrouped by plasmodium species)

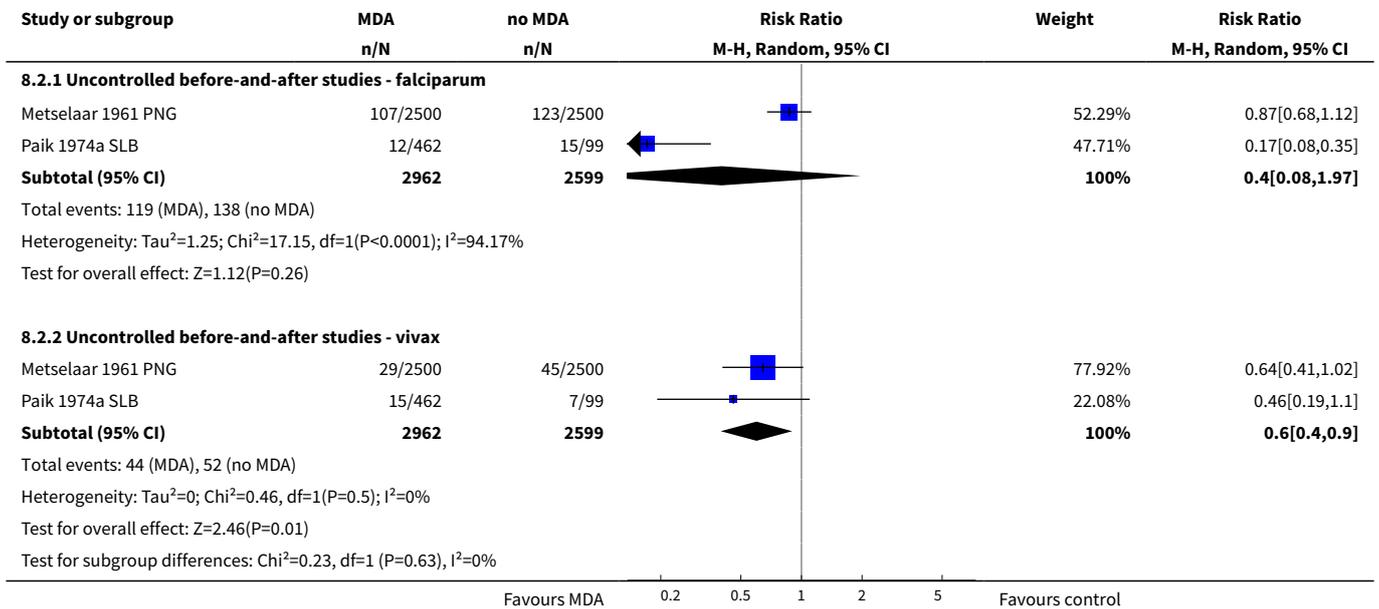
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Parasitaemia Prevalence at baseline	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Non-randomized controlled studies - falciparum	2	1537	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.03, 1.74]
1.2 Non-randomized controlled studies - vivax	2	1537	Risk Ratio (M-H, Random, 95% CI)	3.84 [1.33, 11.04]
2 Parasitaemia Prevalence during MDA	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Uncontrolled before-and-after studies - falciparum	2	5561	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.08, 1.97]
2.2 Uncontrolled before-and-after studies - vivax	2	5561	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.40, 0.90]
3 Parasitaemia Prevalence <1 month post MDA	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Non-randomized controlled studies - falciparum	1	433	Risk Ratio (M-H, Random, 95% CI)	0.02 [0.00, 0.08]
3.2 Non-randomized controlled studies - vivax	1	433	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.82]
3.3 Uncontrolled before-and-after studies - falciparum	4	7367	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.18, 0.29]
3.4 Uncontrolled before-and-after studies - vivax	4	7367	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.41, 0.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Parasitaemia Prevalence 1-3 months post MDA	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Non-randomized controlled studies - falciparum	1	357	Risk Ratio (M-H, Random, 95% CI)	0.03 [0.01, 0.12]
4.2 Non-randomized controlled studies - vivax	1	357	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.46, 4.11]
4.3 Uncontrolled before-and-after studies - falciparum	2	5754	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.09, 0.51]
4.4 Uncontrolled before-and-after studies - vivax	2	5754	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.32, 0.76]
5 Parasitaemia Prevalence 4-6 months post MDA	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Non-randomized controlled studies - falciparum	1	410	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.14, 0.33]
5.2 Non-randomized controlled studies - vivax	1	410	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.31, 2.08]
5.3 Uncontrolled before-and-after studies - falciparum	2	3642	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.13, 1.23]
5.4 Uncontrolled before-and-after studies - vivax	2	3642	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.24, 0.39]
6 Parasitaemia Prevalence >12 months post MDA	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Non-randomized controlled studies - falciparum	1	1331	Risk Ratio (M-H, Random, 95% CI)	0.01 [0.00, 0.13]
6.2 Non-randomized controlled studies - vivax	1	1331	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.15, 0.86]
6.3 Uncontrolled before-and-after studies - falciparum	2	5884	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.04, 0.09]
6.4 Uncontrolled before-and-after studies - vivax	2	5884	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.12, 0.24]

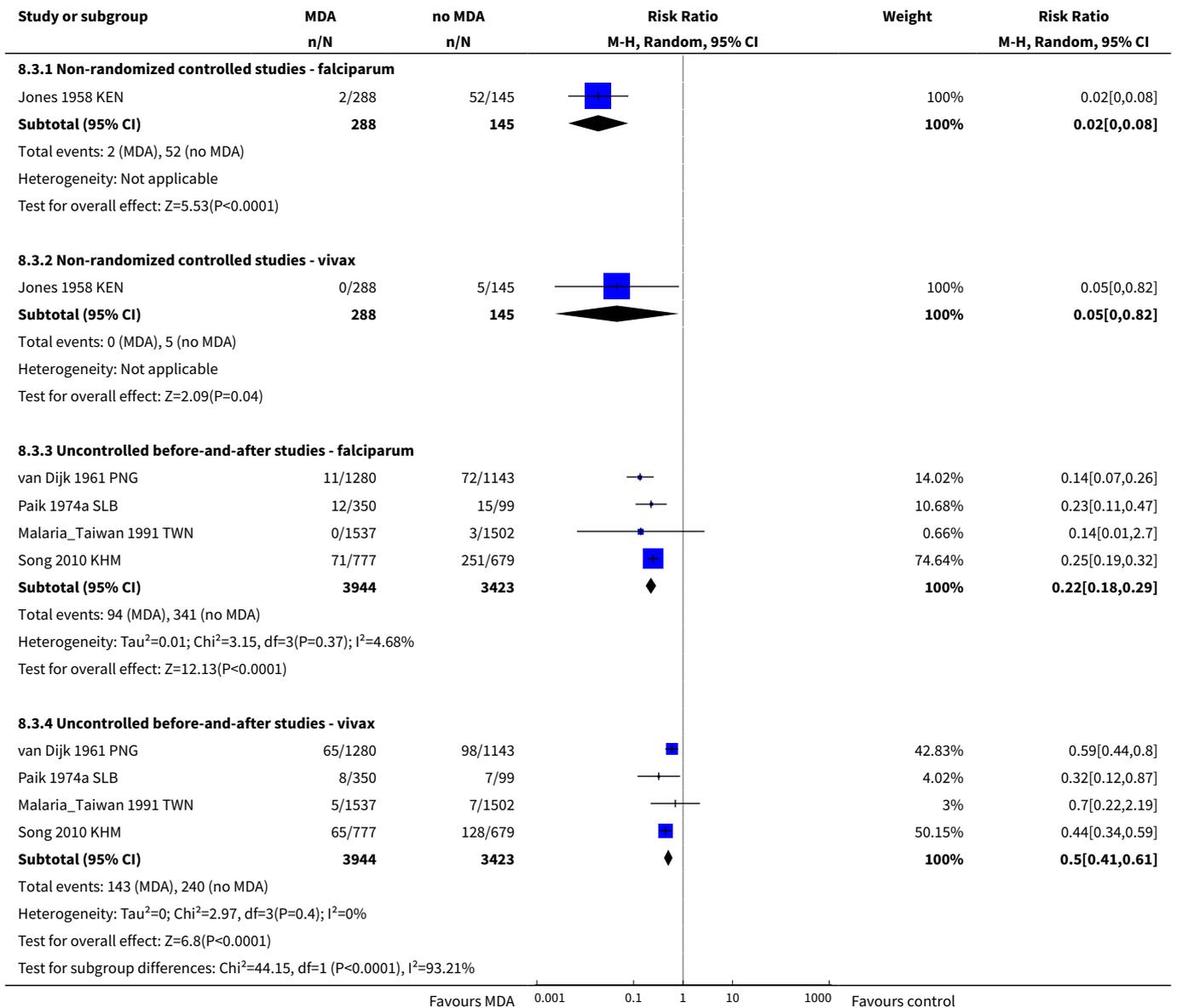
Analysis 8.1. Comparison 8 MDA versus no MDA for all endemicity levels (Stratified by study design; subgrouped by plasmodium species), Outcome 1 Parasitaemia Prevalence at baseline.



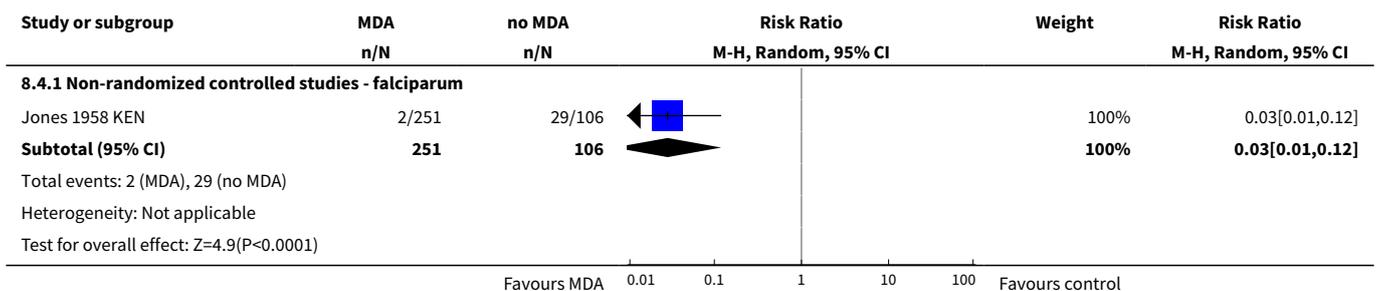
Analysis 8.2. Comparison 8 MDA versus no MDA for all endemicity levels (Stratified by study design; subgrouped by plasmodium species), Outcome 2 Parasitaemia Prevalence during MDA.

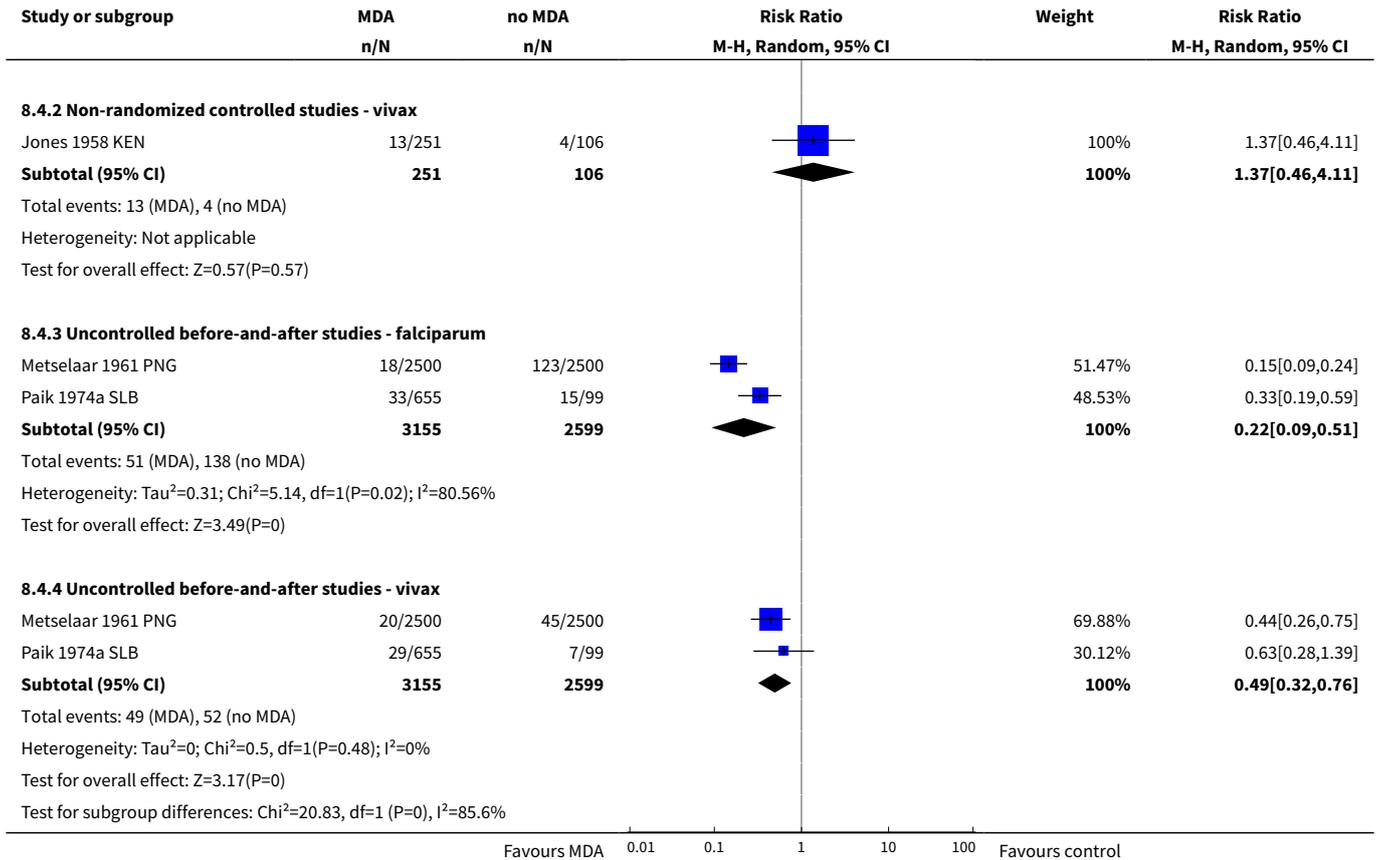


Analysis 8.3. Comparison 8 MDA versus no MDA for all endemicity levels (Stratified by study design; subgrouped by plasmodium species), Outcome 3 Parasitaemia Prevalence <1 month post MDA.

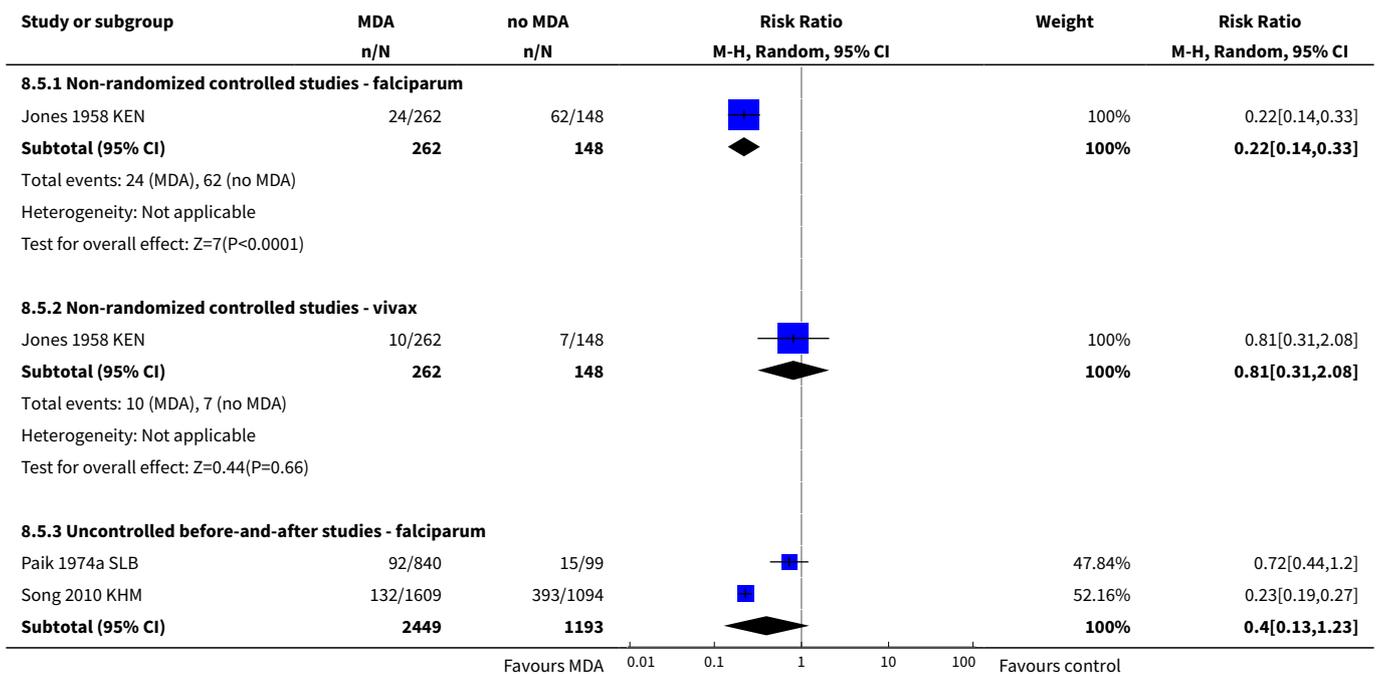


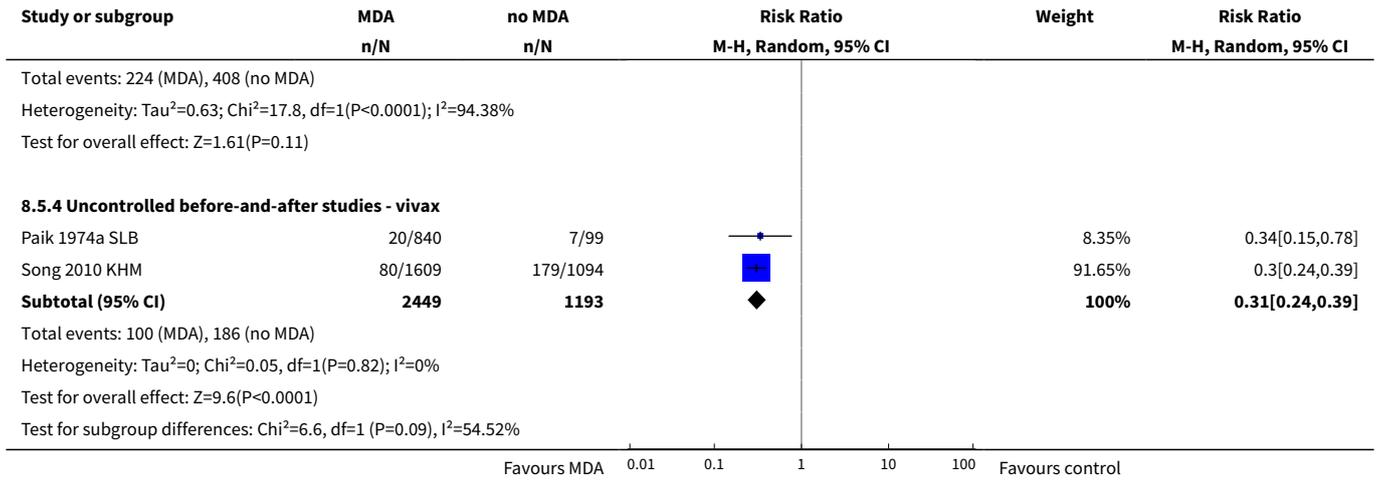
Analysis 8.4. Comparison 8 MDA versus no MDA for all endemicity levels (Stratified by study design; subgrouped by plasmodium species), Outcome 4 Parasitaemia Prevalence 1-3 months post MDA.



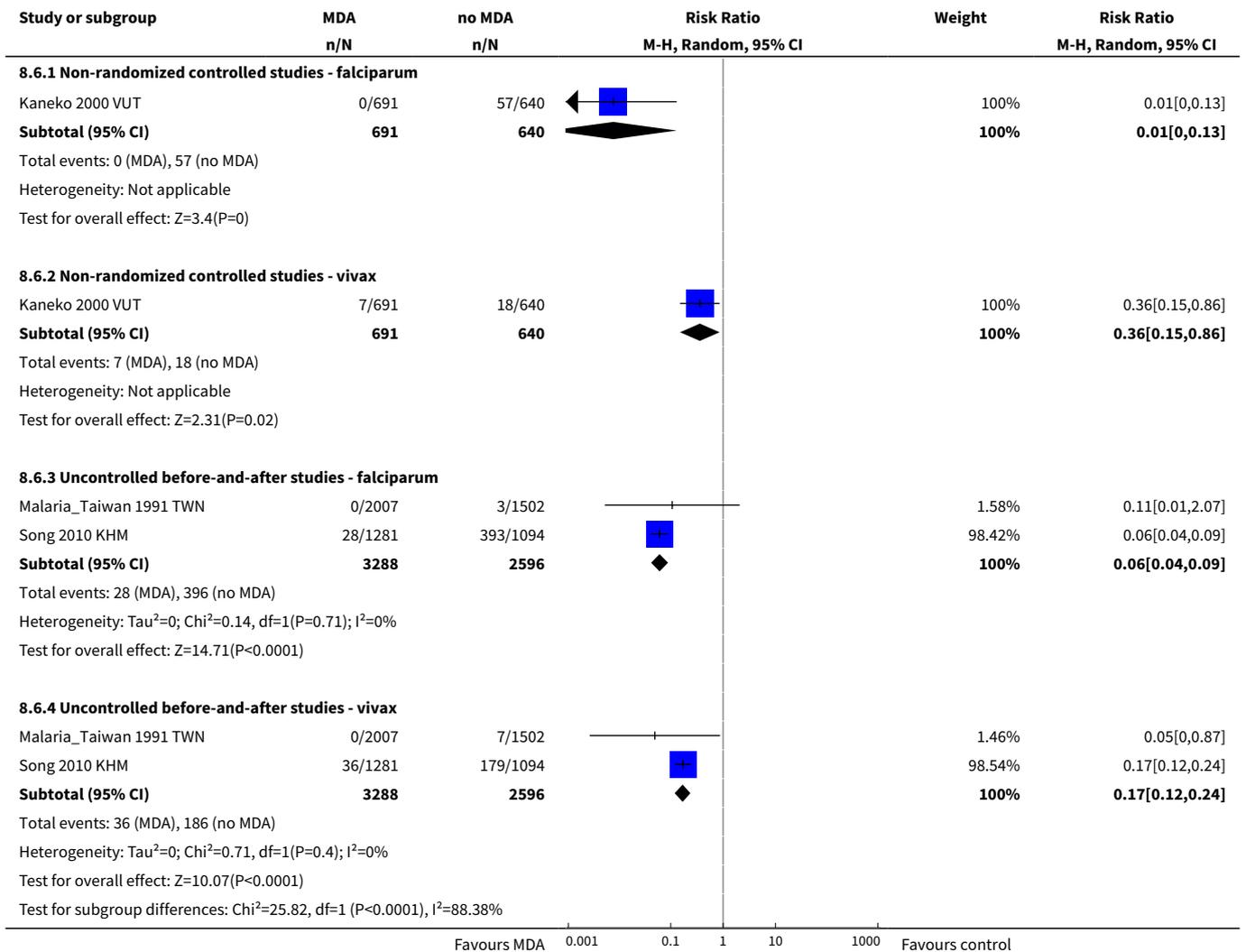


Analysis 8.5. Comparison 8 MDA versus no MDA for all endemicity levels (Stratified by study design; subgrouped by plasmodium species), Outcome 5 Parasitaemia Prevalence 4-6 months post MDA.





Analysis 8.6. Comparison 8 MDA versus no MDA for all endemicity levels (Stratified by study design; subgrouped by plasmodium species), Outcome 6 Parasitaemia Prevalence >12 months post MDA.



ADDITIONAL TABLES

Table 1. Overview of studies conducted in areas of low endemicity

Study ID	De- sign	Coun- try	Year	En- demic- ity	MDA group					Control group/ Baseline	
					Drug (dose)	In- ter- val	No. of rounds	Popula- tion targeted	Cov- er- age	Co-interven- tion	
Shekalaghe 2011	CRT	Tanza- nia	2008	0%*	AS (4 mg/kg/day for 3 days) +SP (25 mg/1.25 mg on day 1) +PQ (0.75 mg on day 3)	-	1	1110	93%	Background ITN use	Placebo + Background ITN use
Malaria_Tai- wan 1991	BAS	Taiwan	1955	3-4%*	CQ (12 mg/kg)	-	1	1520	ND	IRS	IRS

CRT = Cluster-randomized trial; BAS = Uncontrolled before-and-after study; AS = Artesunate; SP = Sulfadoxine-Pyrimethamine; PQ = Primaquine; CQ = Chloroquine; ND = Not described; IRS = Indoor Residual Spraying.

*In all ages

Table 2. Overview of studies conducted in areas of moderate endemicity

Study ID	De- sign	Country	Year	En- demic- ity	MDA group					Control group/base- line	
					Drug (dose)	Interval	No. of rounds	Popula- tion targeted	Cov- er- age	Co-in- ter- ven- tion	
Najera 1973	N- RCS	Nigeria	1966-68	29%*	CQ (450 mg) + Pyr (45 mg)	2 months	11	52,000	78-92%	IRS	IRS alone
Singh 1953	N- RCS	India	1952-53	22%*	AQ (600 mg)	2 weeks	5	125	ND	None	No interven- tion
Jones 1958	N- RCS	Kenya	1952-53	34%†	Pyr (100 mg)	6 months	3	3721-4500	ND	None	No interven- tion
Roberts 1964	N- RCS	Kenya	1953	28%*	Pyr (50 mg)	-	1	101,000	95%	None	No interven- tion
	N- RCS	Kenya	1954	22%*	Pyr (50 mg)	-	1	99,000	95%	None	No interven- tion
Archibald 1960	BAS	Nigeria	1958	29%†	CQ (600 mg) + Pyr (25 mg)	1 month	5	10,000	ND	IRS	IRS

Table 2. Overview of studies conducted in areas of moderate endemicity (Continued)

Cavalié 1962	BAS	Cameroon	1960-61	20%†	CQ (600 mg) + Pyr (50 mg)	4 months	2	22,500	76-92%	IRS	IRS
Houel 1954	BAS	Morocco	1953	14%†	Pyr (100 mg)	-	1	9999	ND	IRS	IRS
Metselaar 1961	BAS	New Guinea	1958-59	13-21%†	CQ (450 mg) +Pyr (50 mg)	1 week	6	2500	90%	IRS	IRS
Jones 1954	BAS	Kenya	1952-53	35%†	Pyr (100 mg)	6 months	3	3721	ND	None	-
van Dijk 1961	BAS	Papua New Guinea	1960	39%†	CQ (450 mg)	4 weeks	11	1250	97%	None	-
Comer 1971	BAS	Panama	1965-68	17%*	Pyr (50 mg / 75 mg) + PQ (40 mg)	2 weeks	49	1709	61-87%	None	-

N-RCS = Non-randomized controlled study; BAS = Uncontrolled before-and-after study; AQ = Amodiaquine; Pyr = Pyrimethamine; CQ = Chloroquine; PQ = Primaquine; ND = Not described; IRS = Indoor Residual Spraying.

*In all ages

†Amongst children only

Table 3. Overview of studies conducted in areas of high endemicity

Study ID	De- sign	Country	Year	En- demic- ity	MDA group Drug (dose)	Interval	No. of round- targeted	Popu- lation	Cov- er- age	Co- in- ter- ven- tion	Control group
Von Seidlein 2003	CRT	Gambia	1999	43%†	AS (4 mg/kg/day for 3 days) +SP (25 mg/1.25 mg on day 1)	-	1	1969	89%	None	Placebo
Molineaux 1980	N- RCS	Nigeria	1970-75	46%*	SP (500 mg/25 mg)	10 weeks	9‡	14,129	85%	IRS	IRS alone
					SP (500 mg/25 mg)	2-10 weeks	23‡	1810	85%	IRS	IRS alone
Escudie 1962	N- RCS	Burkina Faso	1960-61	56.1%†	CQ (600 mg)/AQ (600 mg) +PQ (15 mg)	1 month	8	1890	75-92%	None	No inter- vention

Table 3. Overview of studies conducted in areas of high endemicity (Continued)

					CQ (600 mg)/AQ (600 mg) +PQ (15 mg)	2 weeks	15	2560	84-97%	None	No inter- vention
					CQ (600 mg)/AQ (600 mg) +PQ (15 mg)	1 month	8	5400	81-92%	IRS	IRS alone-
					CQ (600 mg)/AQ (600 mg) +PQ (15 mg)	2 weeks	15	3490	82-94%	IRS	IRS alone-
Schneider 1961	N- RCS	Burkina Faso	1960-61	59%†	CQ (600 mg)/AQ (600 mg) +PQ (15 mg)	2 weeks	15	2500	90%	None	No inter- vention
Archibald 1960	BAS	Nigeria	1957-59	64%†	CQ (600 mg) +Pyr (25 mg)	6 months	4	1300	ND	IRS	IRS-
Cavalié 1962	BAS	Cameroon	1960-61	65%*	CQ (600 mg) +Pyr (50 mg)	-	1	7000	100%	IRS	IRS
Gaud 1953	BAS	Morocco	1952	42%*	AQ (600 mg)	-	1	3000	ND	None	-
Ricosse 1959	BAS	Burkina Faso	1958-59	56%†	Pyr (50 mg)	2 weeks	8	3000	82-91%	None	-
Song 2010	BAS	Cambo- dia	2003-06	56%†	AS (125 mg/day for 2 days) + PIP (750 mg/day for 2 days) + PQ (9 mg every 10 days)	-	1	3653	ND	None	-
Hii 1987	BAS	Malaysia	1984-85	56%†	SP (1500 mg / 75 mg) + PQ (30 mg)	-	1	148	76%	None	-
Kligler 1931	BAS	Pales- tine	1930	67%†	Plas (30 mg) + Q (900 mg) twice daily for 5 days	3 weeks	3	953	79%	None	-

CRT= Cluster-randomized trial; N-RCS = Non-randomized controlled study; BAS = Uncontrolled before-and-after study; AS = Artesunate; SP = Sulfadoxine (or sulfalene)-Pyrimethamine; Pyr = Pyrimethamine; CQ = Chloroquine; AQ = Amodiaquine; PQ = Primaquine; Pip = Piperaquine; Plas = Plasmochin; Q = Quinine; ND = Not described; IRS = Indoor Residual Spraying.

*In all ages

†Amongst children only

‡Estimated from the data provided

Table 4. Overview of studies comparing MDA + vector control versus no intervention

Study ID	De- sign	Country	Year	En- demic- ity	MDA group Drug (dose)	Interval	No. Popu- lation rounds	Cov- er- age	Co-in- ter-	Control group/ baseline
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Table 4. Overview of studies comparing MDA + vector control versus no intervention (Continued)

								tar- geted		ven- tion	
Moderate Endemicity											
Kaneko 2000	N- RCS	Vanuatu	1991-99	29%*	CQ (600 mg) + SP (1500 mg/75 mg) + PQ (45 mg) weeks 1, 5, and 9; CQ (300 mg) + PQ (45 mg) weeks 2, 3, 4, 6, 7, and 8	1 week	9	718	79-92%	ITN + larvivorous fish	low base-line coverage of ITNs
Ricosse 1959	BAS	Burkina Faso	1958-59	15%†	Pyr (50 mg)	2 weeks	8	5000	82-91%	IRS	None
De Zulueta 1961	BAS	Uganda	1959-60	34%†	CQ (600 mg) + Pyr (50 mg)	3 months	4	30,384	80%	IRS	None
De Zulueta 1964	BAS	Uganda	1960	23%†	CQ (600 mg) + Pyr (50 mg)	5 months	2	16,000	50%	IRS	None
Paik 1974a	BAS	Solomon Islands	1972	28%*	CQ (600 mg) +Pyr (50 mg)	1 month	4	ND	90%	IRS	None
High Endemicity											
Molineaux 1980	N- RCS	Nigeria	1970-75	46%*	SP (500 mg/25 mg)	10 weeks	9‡	14,129	85%	IRS	None
					SP (500 mg/25 mg)	2-10 weeks	23‡	1810	85%	IRS	None
Escudie 1962	N- RCS	Burkina Faso	1960-61	56.1%†	CQ (600 mg) /AQ (600 mg) + PQ (15 mg)	1 month	8	5400	81-92%	IRS	None
					CQ (600 mg)/AQ (600 mg) + PQ (15 mg)	2 weeks	15	3490	82-94%	IRS	None
Schneider 1961	N- RCS	Burkina Faso	1960-61	59%†	AQ (600 mg) + PQ (15 mg)	2 weeks	8	3525	ND	IRS	None
Metselaar 1961	BAS	New Guinea	1958-59	46%*	CQ (450 mg) +Pyr (50 mg)	1 week	6	2500	90%	IRS	None
Hii 1987	BAS	Malaysia	1984-85	46%†	SP (1500 mg / 75 mg) + PQ (30 mg)	-	1	754	87%	ITN	None

N-RCS = Non-randomized controlled study; BAS = Uncontrolled before-and-after study; AQ = Amodiaquine; Pyr = Pyrimethamine; CQ = Chloroquine; SP = Sulfadoxine (or sulfalene)-Pyrimethamine; PQ = Primaquine; ND = Not described; IRS = Indoor Residual Spraying; ITN = Insecticide Treated Net.

*In all ages
†Amongst children only
‡Estimated from the data provided

Table 5. Overview of studies assessing parasitaemia incidence only

Study ID	De- sign	Country	Year	Baseline Incidence	MDA group					Base- line	
					Drug (dose)	In- ter- val	No. Popula- tion roundtargeted	Cov- er- age	Co-inter- vention		
Garfield 1983	BAS	Nicaragua	1981-82	0.4/1000	CQ (500 mg/day for 3 days) + PQ (15 mg/day for 3 days)	-	1	2,300,000	70-80%	Larval control	None
Simeons 1938	BAS	India	1935	156/1000	Ate (300 mg) + Plas (60 mg)	-	1	5650	100%	Larval control	None
Gabaldon 1959	BAS	Venezuela	1956-57	0.4/1000	Pyr (50 mg)	1 week	24	111,995	ND	IRS	IRS
Kondrashin 1985	BAS	India	1981	4/1000	CQ (600 mg) + PQ (45 mg)	6 months	2	51,325	85%	IRS	IRS
Paik 1974b	BAS	Solomon Islands	1972-73	15/1000	CQ (300 mg/day for 5 days) + PQ (15 mg/day for 5 days)	3 months	3	1200	90%	None	-
Cáceres Garcia 2008	BAS	Venezuela	2002-07	22/1000	CQ (25 mg/kg over 3 days) +PQ (3.5 mg/kg over 7 days)	-	1	22,941	77%	None	-

BAS = Uncontrolled before-and-after study; PQ = Primaquine; CQ = Chloroquine; Pyr = Pyrimethamine; Plas = Plasmochin; Ate = Atebrin; ND = Not described; IRS = Indoor Residual Spraying.

†Amongst children only

Table 6. Summary of findings table: Mass drug administration in areas of low endemicity (≤5%)

Mass drug administration in areas of low endemicity
Patient or population: People living in malaria endemic areas
Settings: Areas with low (≤5%) endemicity
Intervention: Mass drug administration (any regimen)
Comparison: Placebo or no intervention (or baseline data in before-and-after studies)

Table 6. Summary of findings table: Mass drug administration in areas of low endemicity ($\leq 5\%$) (Continued)

Timepoint post MDA	Outcomes	Study design	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of studies	Quality of the evidence (GRADE)
			Assumed risk	Corresponding risk			
			Control	MDA			
<1 month	Parasite prevalence	Before-and-after	50 per 1000 ¹	14 per 1000 (7 to 25)	RR 0.27 (0.14 to 0.50)	1 study	⊕⊕⊕⊕ very low ^{2,3,4,5}
	Parasite incidence	-	-	-	-	0 studies	-
	Gametocyte prevalence	-	-	-	-	0 studies ²	-
12 months	Parasite prevalence	Before-and-after	50 per 1000 ¹	1 per 1000 (0 to 6)	RR 0.02 (0 to 0.12)	1 study	⊕⊕⊕⊕ very low ^{2,3,4,5}
	Parasite incidence	-	-	-	-	0 studies	-
	Gametocyte prevalence	-	-	-	-	0 studies ²	-

The **assumed risk** has been set at 5%. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ For illustrative purposes the control group prevalence has been set at 5%.

² Only one cluster-randomized trial from Tanzania has evaluated MDA in a setting of low endemicity and this study recorded no episodes of parasitaemia or gametocytaemia at baseline or throughout six months follow-up in either the control or intervention groups.

³ Downgrade by 1 for serious risk of bias: This study is uncontrolled, and so at very high risk of confounding.

⁴ Downgraded by 1 for serious indirectness: This single study from Taiwan reported the effects of MDA administered as a single dose of chloroquine (12 mg/kg). Further trials are needed from a variety of settings to have confidence in the results.

⁵ Compared to baseline data a large reduction in parasite prevalence was seen at 1 month and 12 months post-MDA.

Table 7. Summary of findings table: Mass drug administration in areas of moderate endemicity (6 to 39%)

Mass drug administration in areas of moderate endemicity							
Patient or population: People living in malaria endemic areas							
Settings: Areas with moderate malaria endemicity (6-39%)							
Intervention: Mass drug administration (any regimen)							
Comparison: No intervention (or baseline data in before-and-after studies)							
Timepoint post MDA	Outcomes	Study design	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of studies	Quality of the evidence (GRADE)
			Assumed risk	Corresponding risk			
			Control	MDA			
<1 month	Parasitaemia prevalence	Non-randomized	250 per 1000	5 per 1000 (3 to 15)	RR 0.03 (0.01 to 0.08)	3 studies	⊕⊕⊕⊕ moderate 1,2,3,4
		Before-and-after	250 per 1000	73 per 1000 (43 to 120)	RR 0.29 (0.17 to 0.48)	3 studies	⊕⊕⊕⊕ low 5,3,6
	Parasitaemia incidence	-	-	-	-	0 studies	-
	Gametocyaemia prevalence	Non-randomized	100 per 1000	28 per 1000 (10 to 82)	RR 0.28 (0.1 to 0.82)	1 study	⊕⊕⊕⊕ very low 1,7
		Before-and-after	100 per 1000	47 per 1000 (25 to 87)	RR 0.47 (0.25 to 0.87)	3 studies	⊕⊕⊕⊕ low 5,6,8
	4-6 months	Parasitaemia prevalence	Non-randomized	250 per 1000	70 per 1000 (53 to 95)	RR 0.18 (0.10 to 0.33)	2 studies
Before-and-after			250 per 1000	438 per 1000 (103 to 1000)	RR 1.75 (0.41 to 7.41)	2 studies	⊕⊕⊕⊕ very low 5,10,11
Parasitaemia incidence		-	-	-	-	0 studies	-
Gametocyaemia prevalence		Non-randomized	100 per 1000	52 per 1000 (24 to 111)	RR 0.52 (0.24 to 1.11)	1 study	⊕⊕⊕⊕ very low 12

Table 7. Summary of findings table: Mass drug administration in areas of moderate endemicity (6 to 39%) (Continued)

Before-and-after	100 per 1000	35 per 1000 (12 to 101)	RR 0.35 (0.12 to 1.01)	1 study	⊕⊕⊕⊕ very low ¹²
The assumed risk for parasitaemia prevalence has been set at 25%. Gametocytaemia prevalence was generally lower in the included studies and the assumed risk has therefore been set at 10%.					
The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk Ratio.					
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.					

- ¹ No serious risk of bias: Although there were some differences in prevalence at baseline, these were much smaller in size than the large effects seen post-intervention.
- ² No serious indirectness: These three studies were conducted in Kenya in 1953 and 1954 (pyrimethamine administered every six months for three rounds), and in India in 1953 (amodiaquine administered every two weeks for five rounds). A fourth study from Nigeria in 1973 reported a similar reduction in prevalence during an ongoing MDA program. Although these studies are old, similar effects might be expected today with effective anti-malarials.
- ³ No serious inconsistency: Consistent and large reductions were seen in these studies.
- ⁴ Upgraded by 1 for large effect size: Very large effects were seen consistently across both controlled and uncontrolled studies.
- ⁵ No serious risk of bias: These studies are uncontrolled, and so are at very high risk of confounding. However, as the GRADE approach automatically downgrades non-randomized controlled studies by two levels for risk of bias we did not further downgrade.
- ⁶ No serious indirectness: These three studies were conducted between 1953 and 1961, and administered MDA as: Pyrimethamine once only (Morocco), chloroquine plus pyrimethamine every month for five rounds (Nigeria) and chloroquine every four weeks for 11 rounds (Papua New Guinea). Although these studies are old, similar effects might be expected today with effective anti-malarials.
- ⁷ Downgraded by 1 for serious indirectness: This single trial in Kenya gave pyrimethamine every six months for three rounds. Different regimens may have different effects and primaquine, a drug with gametocytocidal properties, was not given. One further trial from Nigeria in the 1960s, which only reported on prevalence during an ongoing MDA programme, also administered MDA without primaquine.
- ⁸ No serious inconsistency: Gametocyte prevalence was lower post-intervention in all four trials, however there was variation in the size of this effect.
- ⁹ No serious indirectness: These two studies are both from Kenya in the 1950s, and both administer MDA as pyrimethamine alone. One study continued follow-up for > 6 months when an effect was still present.
- ¹⁰ No serious indirectness: These two studies were conducted between 1959 and 1961, and administered MDA as: chloroquine plus pyrimethamine every four months for two rounds (Cameroon), chloroquine plus pyrimethamine every month for five rounds (Nigeria).
- ¹¹ Downgraded by 1 for serious inconsistency: At this time point results were mixed. One study found a higher prevalence at this time point and one found no difference.
- ¹² Downgraded by 1 for serious indirectness: This single trial found no substantial difference between groups at 4-6 months. Modern trials with different regimens may have different effects. This study did not administer primaquine as part of MDA.

Table 8. Summary of findings table: Mass drug administration in areas of high endemicity (≥40%)

Mass drug administration in areas of high endemicity

Table 8. Summary of findings table: Mass drug administration in areas of high endemicity ($\geq 40\%$) (Continued)

Patient or population: People living in malaria endemic areas
Settings: Areas with high malaria endemicity ($\geq 40\%$)
Intervention: Mass drug administration (any regimen)
Comparison: No intervention (or baseline data in before-and-after studies)

Timepoint post MDA	Outcomes	Study design	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of studies	Quality of the evidence (GRADE)
			Assumed risk	Corresponding risk			
			Control	MDA			
< 1 month	Para-sitaemia prevalence	Cluster-randomized	500 per 1000	410 per 1000 (335 to 505)	RR 0.82 (0.67 to 1.01)	1 study	⊕⊕⊕⊕ low 1,2,3
		Non-randomized	500 per 1000	85 per 1000 (50 to 140)	RR 0.17 (0.10 to 0.28)	3 studies	⊕⊕⊕⊕ moderate 4,5,6,7
		Before-and-after	500 per 1000	185 per 1000 (140 to 245)	RR 0.37 (0.28 to 0.49)	4 studies	⊕⊕⊕⊕ low 8,9,10
	Para-sitaemia incidence	Cluster-randomized	60 per 1000	25 per 1000 (14 to 44)	RR 0.41 (0.23 to 0.73)	1 study	⊕⊕⊕⊕ moderate 1,2,11
		Non-randomized	100 per 1000	16 per 1000 (8 to 30)	RR 0.16 (0.08 to 0.30)	3 studies	⊕⊕⊕⊕ moderate 4,5,6,7
			Before-and-after	100 per 1000	38 per 1000 (13 to 108)	RR 0.38 (0.13 to 1.08)	3 studies
4-6 months	Para-sitaemia prevalence	Cluster-randomized	500 per 1000	580 per 1000 (465 to 720)	RR 1.16 (0.93 to 1.44)	1 study	⊕⊕⊕⊕ moderate 1,2,13
		Non-randomized	-	-	-	0 studies	-
		Before-and-after	500 per 1000	205 per 1000 (120 to 360)	RR 0.41 (0.24 to 0.72)	3 studies	⊕⊕⊕⊕ low 8,14
	Para-sitaemia	Cluster-randomized	60 per 1000	67 per 1000 (52 to 85)	RR 1.11 (0.87 to 1.41)	1 study	⊕⊕⊕⊕ moderate 1,2,13

Table 8. Summary of findings table: Mass drug administration in areas of high endemicity ($\geq 40\%$) (Continued)

incidence						
Gametocyt- aemia prevalence	Cluster-randomized	100 per 1000	107 per 1000 (62 to 185)	RR 1.07 (0.62 to 1.85)	1 study	⊕⊕⊕⊕ low 1,2,3
	Non-randomized	-	-	-	0 studies	-
	Before-and-after	100 per 1000	35 per 1000 (10 to 128)	RR 0.35 (0.10 to 1.28)	2 studies	⊕⊕⊕⊕ very low 8,15

The **assumed risk** for parasitaemia prevalence has been set at 50%. Gametocyt-
aemia prevalence was generally lower in the included studies and the **assumed risk** has
therefore been set at 10%. The **assumed risk** for parasitaemia incidence is taken from the control group of the single trial.

The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ No serious risk of bias: This cluster-randomized trial was at low risk of bias.

² Downgraded by 1 for serious indirectness: This single study from the Gambia in 1999 administered MDA as AS+SP. The findings may not be easily generalized to other settings, or to alternative MDA regimens. The first time point measured post-MDA was 1-3 months.

³ Downgraded by 1 for serious imprecision: The result was not statistically significant but the 95% CI is wide and includes important effects.

⁴ No serious risk of bias: Although there was some evidence of baseline imbalance between the intervention and control areas, these were generally of smaller magnitude than the effects seen.

⁵ No serious indirectness: The data presented here were measured during ongoing multiple-round MDA programmes, not at one month post-intervention. The studies were conducted in Burkina Faso in 1961 (CQ or AQ plus PQ every two to four weeks), and Nigeria in 1975 (SP given every two weeks or every 10 weeks). Although these studies are old, similar effects might be expected today with effective anti-malarials.

⁶ No serious inconsistency: The observed effects were consistently large in all three trials.

⁷ Upgraded by 1 for the large effect size: Large effects seen in all trials.

⁸ No serious risk of bias: These studies are uncontrolled, and so are at very high risk of confounding. However, as the GRADE approach automatically downgrades non-randomized controlled studies by two levels for risk of bias we did not further downgrade.

⁹ No serious indirectness: These four studies were conducted in Palestine in 1930 (plasmoquine plus quinine every three weeks for three rounds), Burkina Faso in 1959 (pyrimethamine every two weeks), in Malaysia in 1985 (SP + PQ once only), and Cambodia in 2006 (AS + piperaquine once only plus PQ every 10 days).

¹⁰ No serious inconsistency: Three studies observed large effects, while one small study found no effect.

¹¹ No serious imprecision: The result is statistically significant.

¹² No serious indirectness: Two large studies found large effects in Burkina Faso in the 1950s (pyrimethamine every 2 weeks for 8 rounds), and Palestine in the 1930s (plasmoquine plus quinine every three weeks for three rounds). One small study from Malaysia in the 1980s found no effect.

¹³ No serious imprecision: The 95% CI excludes clinically important reductions at this time point.

- 14 No serious inconsistency: The two large studies from Palestine and Cambodia still demonstrated a large reduction at 4-6 months while the small study from Malaysia found no difference
- 15 Downgraded by 1 for serious indirectness: Benefits beyond three months have only been demonstrated in this single study from Cambodia. MDA was administered as artesunate plus piperazine once only followed by primaquine every 10 days for six months.

APPENDICES

Appendix 1. Search strategy

MEDLINE+

A. Anti-Malarials

exp Antimalarials/ or exp Malaria/ or antimalarial* or anti-malarial* or ((schizonticidal* or gametocidal* or hypnozoiticidal* or drug* or treatment) and (malaria*))

B. Mass Administration

((mass or coordinate*) adj5 (administ* or distribut* or applicat* or "use" or therap* or treatment*))

EMBASE

A. Anti-Malarials

exp antimalarial agent/ or exp malaria/ or antimalarial* or anti-malarial* or ((schizonticidal* or gametocidal* or hypnozoiticidal* or drug* or treatment) and (malaria*))

B. Mass Administration

((mass or coordinate*) adj5 (administ* or distribut* or applicat* or "use" or therap* or treatment*))

COCHRANE LIBRARY

A. Anti-Malarials

(Must run each MeSH term separately. Ovid syntax used for recording purposes.)

exp Antimalarials/ or exp Malaria/ or antimalarial* or anti-malarial* or ((schizonticidal* or gametocidal* or hypnozoiticidal* or drug* or treatment) and (malaria*))

B. Mass Administration

((mass or coordinate*) near/5 (administ* or distribut* or applicat* or "use" or therap* or treatment*))

CAB DIRECT

A. Anti-Malarials

ti=(antimalarial* or anti-malarial* or ((schizonticidal* or gametocidal* or hypnozoiticidal* or drug* or treatment) and (malaria*))) or ab=(antimalarial* or anti-malarial* or ((schizonticidal* or gametocidal* or hypnozoiticidal* or drug* or treatment) and (malaria*))) or de="antimalarials"

B. Mass Administration

(mass) and (administ* or distribut* or applicat*)

LILACS

A. Anti-Malarials

antimalarial* or anti-malarial* or ((schizonticidal* or gametocidal* or hypnozoiticidal* or drug* or treatment) and (malaria*))

CONTRIBUTIONS OF AUTHORS

EP, JH and JS reviewed the literature and abstracted the data. EP, JH, JS and DS conducted the analyses. EP, JH and DS drafted the manuscript. All authors contributed to the design of the review and reviewed the manuscript.

DECLARATIONS OF INTEREST

All authors report no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Centers for Disease Control and Prevention, USA.

External sources

- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Authors and contact person

Since the initial publication of our protocol, there have been changes in the order of authorship and in the designated contact person. Jimée Hwang will now act as the contact person for this review, to whom correspondence about the review should be addressed. Order of authorship has changed, with Jimée Hwang as senior author and Jacek Skarbinski listed as second author.

Study Design

Clinical illness was not assessed as an outcome measure, as initially planned in the original protocol. However, the methods for extracting and analyzing all other primary and secondary outcomes followed the methods outlined in the protocol.

Adjustments for cluster randomized trials were not attempted and estimates were individually analyzed.

Methodological quality was assessed using the Cochrane Collaboration's risk of bias tool ([Higgins 2011](#)) and suggested risk of bias criteria for Effective Practice and Organisation of Care (EPOC) reviews. A GRADE assessment was also added.

Measures of treatment effect

Due to the few high-quality trials and the heterogeneity of our studies, funnel plots were not created to examine study effect by plotting relative measures of treatment effect on a logarithmic scale against the standard error (and its inverse).

We did not categorize our outcomes as early outcome measures (< 6 months after MDA) versus late outcome measures (\geq 6 months after MDA). Instead, we created smaller time intervals (eg during, within 1 month, 1-3 months, 4-6 months, 7-12 months, and >12 months post-intervention) due to the heterogeneity of our studies and early outcome measures.

Due to the small number of studies in our proposed subgroup analyses, we did not carry out analyses assessing high and moderate quality studies only, or review the use of MDA with chloroquine/primaquine for control of *P. vivax*.

INDEX TERMS

Medical Subject Headings (MeSH)

*Endemic Diseases; Antimalarials [*administration & dosage] [adverse effects]; Disease Eradication [methods]; Malaria [*drug therapy]; Parasitemia [*drug therapy]; Program Evaluation

MeSH check words

Humans